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A Special Issue

Birth of a New Drug

Devoted to the story of modern pharmaceutical science applied to the development of therapeutic agents

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BIRTH OF A NEW DRUG . . . AN INTRODUCTION

RELATIVELY few men may see at first hand, with clarity and completeness, the exquisitely wrought structure of pharmaceutical science upon which reputable drugs solidly rest. This modern structure is erected by hands and tools from many fields. For general practitioners of pharmacy or medicine, immersed in the urgent task of ministering to the ill, the majestic pattern of research may be distorted by time, space and a hurried glance. For those in highly specialized work the broad view may be blocked by myopic concentration on the task at hand.

To bring the integrated structure of modern pharmaceutical and medical science into focus, the AMERICAN PHARMACEUTICAL ASSOCIATION presents this special issue of the JOURNAL on "The Birth of a New Drug." It is designed for the majority of us whose day to day concern lies mainly in the postnatal development and use of new drugs in medical care. The authors have attempted—successfully, we believe—to present a readable, concise story of modern drug development, a subject that might well fill several volumes. But no attempt has been made to offer technical details to the investigator. No advice is proffered to those interested in production and marketing.

This issue was planned for the practicing pharmacist, although we hope that all students of the health professions may find it useful. We have the feeling that the pharmacist interested enough to browse through these pages will find it worth while to stay and read. As one of the authors has pointed out, nothing of so great importance to human welfare is used more completely on faith than a medicinal product. This represents an impelling reason why the pharmacist should understand fully the scientific structure that should support a new therapeutic agent on his shelves. Such information enables the pharmacist to interpret his products and services more intelligently to the physician and to the layman.

Members of the health professions have been cut off rather quickly from the centuries of empiricism and the time when lone investigators attacked major problems, largely isolated scientifically. In attending the "Birth of a New Drug" we were struck by the contrast of today's coordinated research employing complex techniques, which may involve cooperative effort not only among individuals but among sciences, institutions, and nations. A close-up view of this modern scientific structure not only justifies our faith in the products that evolve from it, but lends credence to the era of pharmacy and medicine promised for the future.—THE EDITOR

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by

ROBERT P. FISCHELIS

Secretary
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STRAIGHT *from* HEADQUARTERS

THE principal reason why so many time-honored drugs have become outmoded in our lifetime will be clear to the most casual reader of the material that will appear in this issue on modern drug development. Although pharmaceutical science is firmly based on wisdom acquired in past generations, the modern development of more effective research techniques has had a direct relationship to the influx of more effective therapeutic agents. One of the most important of these techniques has been the coordination of work in many laboratories by many types of investigators for a concentrated attack on complex problems.

Nation-wide cooperative research programs of the war years brought this method to full development. Its recognized advantages in bringing better drugs to the patient much sooner than could otherwise be expected indicate that this research procedure must be continued in some manner.

Yet the availability of effective, properly prepared drugs has never meant that the public will not be plied with misrepresented or worthless remedies offered by those unwilling or unable to follow the guideposts set up by modern pharmaceutical science.

It is in this field that food and drug legislation has played such an important role. Prior to the passage of the Federal Food and Drug Act of 1906 the control of the quality and trueness to label of drugs and medicines was largely a matter of state regulation. Some states were pioneers in the control and prevention of adulteration and misbranding of pharmaceutical products. But the passage of the Food and Drug Act of 1906 constituted the first great step toward adequate protection to the public in a field where the gullible and uninformed must depend largely upon the conscience and ethics of those who know or should know the possibilities and limitations of drugs.

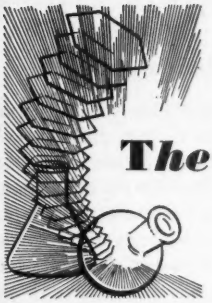
Certain inadequacies of the 1906 Food and Drug Act were corrected only after many years of effort, when the Food, Drug and Cosmetic Act of 1938 was finally enacted. It is doubtful whether some of the more drastic provisions of this Act ever could have been passed, had it not been for the tragic loss of life resulting from a carelessly and improperly formulated drug product. The public outcry at that time forced the inclusion in the new Food, Drug and Cosmetic Act of a provision for establishing the safety of all "new drugs," before they are placed upon the market.

Previously, the painstaking effort necessary to establish the safety and efficacy of drugs before making them available to the sick was made only by conscientious and well equipped manufacturers. Since passage of the 1938 Act it has become routine for all who wish to place a new drug or preparation on the market.

Launching a new drug today is a highly complicated and expensive procedure. The experts who discuss various phases of the subject in this issue provide the strongest evidence that the American people are well protected against possible harm from careless manufacture or lack of knowledge of possible side effects resulting from the administration of new remedies.

Many manufacturing laboratories go far beyond minimum requirements of the Food, Drug and Cosmetic Act related to developmental work, plant facilities, quality control and clinical testing. More and more of those once dubious about "government interference" are recognizing that the Act offers protection to the reputable manufacturer as well as to the public. It has removed from reach many products that were harmful, of variable quality or improperly labeled. It has been helpful not only to control nonprofessional distribution, but also to aid the pharmacist and physician in assuring rational, reliable medication for patients.

The Food and Drug Administration has handled the responsibilities assigned to it with a high degree of efficiency and responsiveness to the public welfare. The weak spot in this system of public protection today is the lack, in many states, of new drug regulation at the state level comparable to that which obtains in interstate commerce. This loophole will be closed by the adoption in all states of the uniform State Food, Drug and Cosmetic Act which parallels the provisions of the Federal Act. When this is accomplished the pharmacists of America will be able to point with pride to the infinite care exercised in the production of *all* drugs which they are called upon to dispense. It is a goal that deserves the active support of practicing pharmacists.



The Organic Chemist

by

HORACE A. SHONLE*

WHEN groups of specialists in different fields work together toward a common goal, it is not easy to distinguish where one group's work ends and another's begins. The field of the organic chemist lies chiefly in the analysis and synthesis of chemical compounds which have a carbon skeleton, and his main task in a pharmaceutical laboratory is the production of new synthetic organic chemical compounds having a therapeutic value.

Until 1824, when Wöhler discovered that urea could be made in the laboratory, it was believed that those compounds designated as organic chemicals could be produced only by living cells. During the century and a quarter following Wöhler's discovery, countless tens of thousands of organic compounds have been prepared, and today nature has few secret products the structure of which has not been fathomed by the organic chemist and duplicated in the laboratory.

The scientific development of medicinal drugs has paralleled the development of physical chemistry and the biological sciences. Organic chemical research in the field of medicinal chemistry first started when the organic chemist began to investigate extracts of plant and animal origin which had medicinal use. He found these extracts contained many different compounds, which he had to separate and isolate by the best means available. Once isolated, they were studied to ascertain which one was responsible for the desired effect, and at the same time their chemical nature was often established.

A great deal of information in the field of organic chemistry was thus accumulated through painstaking investigations of the constituents of plant life. After the structure had been determined by the appropriate degradative and analytical procedures, it was confirmed by synthesizing the product in the laboratory and proving that it was identical with the product isolated from natural sources. The latest of the natural products to yield to the ingenuity of the chemist is penicillin, which has been synthesized in extremely small yields in several laboratories. The isolation of the synthetic product has been announced by du Vigneaud.[1]

The work of the organic chemist covers several phases. Development of more efficient ways of producing a drug of proved value, as for example acetylsalicylic acid and sulfathiazole, is a recurrent and ever-necessary task in order to make medicinal drugs more readily available to everyone. The synthetic production of naturally occurring products, such as vitamins and alkaloids, makes us independent of the variability of natural sources of such products. This type of work requires the highest kind of chemical ingenuity. The problems involved lie entirely in the field of the organic chemist and the chemical engineer.

Much work and effort is being continuously directed toward improving currently used drugs to eliminate undesirable side effects, such as the central nervous stimulating action of pressor drugs, or the habit-forming effect of morphine. In instances where an action is too brief, chemical modifications may increase the length of action; or where there is too prolonged an effect, a change in structure may lessen the period of action, as is true with the barbituric acids.

Creation of new synthetic organic compounds having therapeutic value is a more complex phase of the work of the chemist. These new drugs may arise from consideration of the structure and pharmacological responses of natural products, such as alkaloids or hormones, or they may have a structure which is not related to any natural substance. In this instance, the development depends upon the keen observation and the vivid imagination of chemists working in the field of medicinal chemistry or in pure research. The development of novocaine came from the knowledge of the structure of cocaine, while the discovery of the hypnotic action of the barbituric acids was incidental to a research on pyrimidine compounds.

The physiological activity of a compound is an involved function of the chemical and physical structure of the compound, and very slight changes in either may profoundly modify the

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pharmacological effect. The modification of the properties of a drug, or the production of a new synthetic medicinal, brings the chemist in touch with the intricate relationship of chemical structure and physiological effect.

Modifying Chemical Structure

Structural modifications may involve replacing one group with another at a specific point in the molecule, shifting the same group to another position in the parent molecule, saturating valence bonds, modifying the acidity or basicity, or varying the configuration of an asymmetric carbon atom to change the optical rotation.

Sometimes slight changes completely reverse the action of the compound, as is the case when the terminal methyl group of 1-methylamyl ethyl barbituric acid is moved one carbon atom nearer the nucleus to form 1,3-dimethylbutyl ethyl barbituric acid.[2] The latter compound produces convulsions similar to those of strychnine and is fatal at a low dose. These convulsions can be neutralized and the animal's life saved by the administration of the sedative acting isomer, 1-methylamylethyl barbituric acid.

Practically all of the presently used antispasmodics, anticonvulsants, local anesthetics, chemotherapeutic agents, and hypnotics have been products of this type of approach.

The researcher—having gained skill and insight through modifications of the structure and thus the physiological activity of known therapeutic compounds—is now ready to follow up and bring to fruition such advantageous leads as he may discover by close observation of the results of his own work and that of others. The methods used in developing a new lead are similar to those used in expanding and improving a drug of known action. Exploratory work in fundamental research will eventually produce compounds of new and unique therapeutic value.

The organic chemist cannot progress without the cooperation of groups in related fields upon whom he depends for advice and for evaluation of his products, such as the biochemist, bacteriologist, pharmacologist, toxicologist, pharmaceutical chemist, chemical engineer, and clinician. After obtaining advice from men in as many of these fields as are pertinent to the subject of the investigation, the organic chemist continues to keep in close touch with those who are studying the effects of his compound on animals or living organisms. Without ready knowledge of the effect his compound has on life, he could not intelligently proceed with his synthetic program.

Because of efficient methods of production such drugs as acetylsalicylic acid, sulfathiazole, and vitamin B_1 are available at a moderate cost. Many of the details of the current methods of manufacture may be found in the literature, but on the whole the "know-how" rests with the individual manufacturer, although different producers use different techniques to achieve the same end.[3]

Synthetic procedures for the production of *l*-ephedrine, papaverine, and the various vitamins have made us independent of variable natural sources, some of which lie outside the borders of our country. In the development of more efficient methods, chemical and engineering knowledge, skill and imagination are able to solve the problems without recourse to men in other fields of science. One of the interesting current investigations is the development of the synthesis of vitamin A to the point where its manufacture may be commercially feasible. Both American and European investigators have processes which produce biologically active vitamin A.[4]

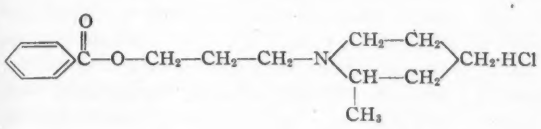
Improving Upon Nature

The procedures followed in the modification of known drugs to increase certain desired therapeutic effects is closedly related to that followed in the elimination of undesired side effects. The broad field of local anesthetics, which started when chemists determined the structure of cocaine, exemplifies this approach.

After the structure of cocaine had been ascertained by degradative procedures and proved by synthesis, the question arose of whether this total structure is necessary for physiological action. Could alterations and amplifications in the structure result in improved action? Could changes be made in the structure which would lessen certain undesirable side actions and toxic effects? It is hardly likely that the metabolic processes of the plant produced various alkaloids and glucosides for a specific physiological action in man. If we go on the basis that the medical usefulness of the plant alkaloids and glucosides is a fortuitous one, then man ought to be able to plan and develop drugs of greater effectiveness and specificity through intelligent study of the structure of these natural products.

"Metycaine"[5] (*see structural formula below*) is a local anesthetic developed for spinal, local infiltrational, and topical anesthesia[6] that resulted from an extensive investigation where the direction of the chemical synthesis was guided by close pharmacological study of the compounds as they

were prepared. In this manner it was possible to ascertain the variations in pharmacological response caused by the introduction of different groups and by substitution in various portions of the alkyl amino alkyl benzoate molecule.



The initiation of the manufacture of this product in 1927–1928 called for chemical intermediates not then available except in laboratory quantities; for example, 2-methyl piperidine, trimethylene chlorohydrin, and 2-methylpiperidinopropyl alcohol. Methods for producing these products in quantity had to be studied and appropriate equipment designed to duplicate the best laboratory yields and to produce a final product that would meet the standards of purity set up for local anesthetics in the U. S. Pharmacopœia.

After "Metycaine" had been in continuous medical use for a number of years, it was included in a series of local anesthetics which were being studied in both surgery and obstetrics by a continuous administration method.[7] Investigators reported that this local anesthetic had unusual properties in the field of caudal analgesia. Here is an example of a new clinical use discovered for a product long after it was on the market.

It is well established that in the evaluation of compounds, such as local anesthetics, when a series is arranged in sequence of effectiveness based on one method of evaluation, different sequences are obtained when other methods are used—for example, subcutaneous, intraspinal, and intracaudal administration, or application to the mucous membrane or eyeball.

"Metycaine" had been selected primarily because of its effectiveness on mucous membranes and its relative low toxicity on subcutaneous administration. It would seem obvious, therefore, to the organic chemist that the original series of local anesthetics should be studied for effectiveness in producing intracaudal analgesia and that additional compounds of related structure should be synthesized and studied. The chemical work involved in this recent investigation[8] gave rise to over one hundred new synthetic compounds, most of which had local anesthetic action, but none of which were as active and as effective for intracaudal analgesia. The project would have stopped there had not the pharmacological group been curious about the action of this series of compounds when evaluated by other criteria. To make a long story short, several compounds were found possessing a modified "Metycaine" structure which had an exceedingly powerful local anesthetic effect on the mucous membrane and on denuded areas of the skin and yet had low toxicity. This again brings up new problems in chemical synthesis, a search for new intermediates, new methods and new equipment.

The development of "Pentamidine," a nonmetallic drug having some value in the treatment of malaria and trypanosomiasis, is an interesting example of the successful development of a drug when the original hypothesis was later found untenable. Two investigators, observing the high carbohydrate requirement of trypanosomes, reasoned that if the blood sugar of experimental animals could be lowered, it might be possible for the animal to eradicate the infection. They therefore treated the infected animals with a guanidine compound capable of lowering blood sugar and, noting that the parasites did disappear, reported their observation. This work was repeated by two other investigators who observed similar results, and likewise ascribed the effect as due to the lowering of the blood sugar, which starved out the parasites.

Dr. Warrington York, director of the Liverpool School of Tropical Medicine, re-examined these interesting observations and found that insulin, which lowers blood sugar, had had no action on the course of the experimental infection and that the guanidine product acted not because it lowered blood sugar but because it had a direct effect on the trypanosomes.

The synthetic chemists could not ask for a better field nor a clearer objective. Close cooperation between the chemists and parasitologists showed that a large number of symmetrical aliphatic diamines, diisothioureas, diguanidines and diamidines had activity against various tropical parasites.[9] The diamidines were the most effective group, with maximum activity found in 4,4′-diamidinodiphenoxypentene, "Pentamidine."

The Search for Antimalarials

In a government sponsored investigation for the development of antimalarial drugs during the war period, American chemists prepared thousands of compounds which were administered to ducks infected with *P. lophurae* and monkeys infected with *P. knowlesi*, since neither birds nor animals can be infected with human malarial parasites. Many of the compounds

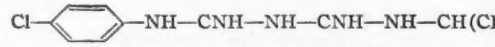
which were found effective in eradicating the experimental malaria were found to have no effect in human malaria.[10]

A number of very active antimalarials containing the quinoline nucleus were prepared in this country. One, "Pentaquine," 6-methoxy-8-(5-isopropylaminoamylamino)-quinoline, can cure cases of relapsing malaria. Several 4-aminoquinolines were found to be very active, but the clinical dose is apt to produce untoward effects. Current investigations are under way to see if these undesired properties are always proportionate to the activity. The chances are that they are not, and so the chemist will place his halogen, methoxy and alkyl groups in different positions in the quinoline nucleus, and compare the relative intensities of these two responses. When, as is almost sure to be the case, a difference is found in the intensities, we will have a lead which can be thoroughly investigated.

One Out of Thousands

Out of the thousands of compounds prepared in dozens of laboratories here and in England, only one new compound of unique structure was found to have a high degree of clinical usefulness. That was the English "Paludrin," which has the structure shown below.

A routine screening test of hundreds of compounds carried out in the English laboratories brought to light the fact that a certain pyrimidine derivative was active against chicken malaria and had a detectable effect on human malaria. This was the 2666th compound investigated. Full chemical attention was turned to this compound, which was taken apart and tested portion by portion, and as a result it was found that the activity resided in the biguanidine portion of the molecule. Next a multitude of related compounds were made and tested on animals and man. By correlating test data and synthetic approaches, the successful product "Paludrin" was obtained, the 4888th compound to be made and tested.[11]

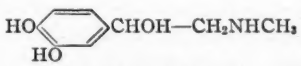


N_1-*p*-chlorophenyl-N_5-isopropylbiguanide

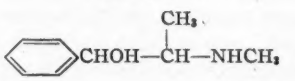
The "sympathomimetic amines" are a varied group of hydrocarbon amines that well illustrate the various phases of the work of the organic chemist and pharmacologist in the field of synthetic medicinals.

Upon administration, this group of drugs exhibits a pharmacological response similar to that produced by the stimulation of the sympathetic nervous system. Some of the members of this series have the additional property of being able to stimulate the central nervous system. There are amines chemically related to this group which cause a drop in blood pressure, instead of the characteristic rise. A few have analgesic action similar to that of aspirin. Several of these properties may be present in the same amine, with the intensity of each varying from compound to compound. In some instances only one property is present in a particular compound. This group has a wide clinical use, being used to support blood pressure, to shrink mucous membrane, and to combat fatigue and depression.

l-Epinephrine, the first of these compounds to be examined and utilized, was found in the adrenal medulla. It was isolated and synthesized by 1904,[12] and quickly found medicinal use. In 1910, Barger and Dale[13] made a thorough study of this compound and some closely related aromatic and some aliphatic amines. In 1923, Chen and his associates[14] re-examined the properties of *l*-ephedrine, one of the alkaloids of the Chinese herb Ma Huang, which had been isolated and obtained in the pure form in 1887. The properties were found to be similar to those of epinephrine.

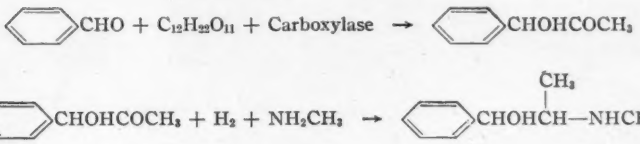


l-Epinephrine



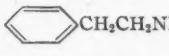
l-Ephedrine

Both these drugs, which are in extensive use today, may be obtained from natural and synthetic sources. The synthesis of *l*-ephedrine is of interest, since it represents a combination of biological and chemical methods. Benzaldehyde is added to a sugar solution, which is then fermented. During this fermentation process, the yeast enzyme, carboxylase, converts the benzaldehyde into the optically active phenylhydroxy acetone. When the latter is catalytically hydrogenated in the presence of methylamine, *l*-ephedrine is obtained. This is a very economical and dependable method of manufacture, inasmuch as the *l*-ephedrine obtained has the correct optical rotation. Consequently, we are no longer dependent upon the casual gathering of a drug-containing plant in a foreign country. The reactions of this synthesis are as follows:



Ephedrine contains two optically active carbon atoms, that is, it has two carbon atoms each of which are attached to four different groups. Because of this, a number of stereoisomers can exist, some of which are relatively inert. Organic synthetic methods of preparing such compounds always result in a mixture of the optical isomers, which is undesirable in that usually only one optical form produces the desired clinical effect. This is circumvented in the case given above for *l*-ephedrine by introducing an asymmetric biological synthetic step.

Chemists have devoted much time to modifying the structure of epinephrine and ephedrine to obtain the maximum degree of a desired pharmacological effect. An inspection of the structures of epinephrine and ephedrine shows that they are both derivatives of phenylethylamine, which itself has pressor action:

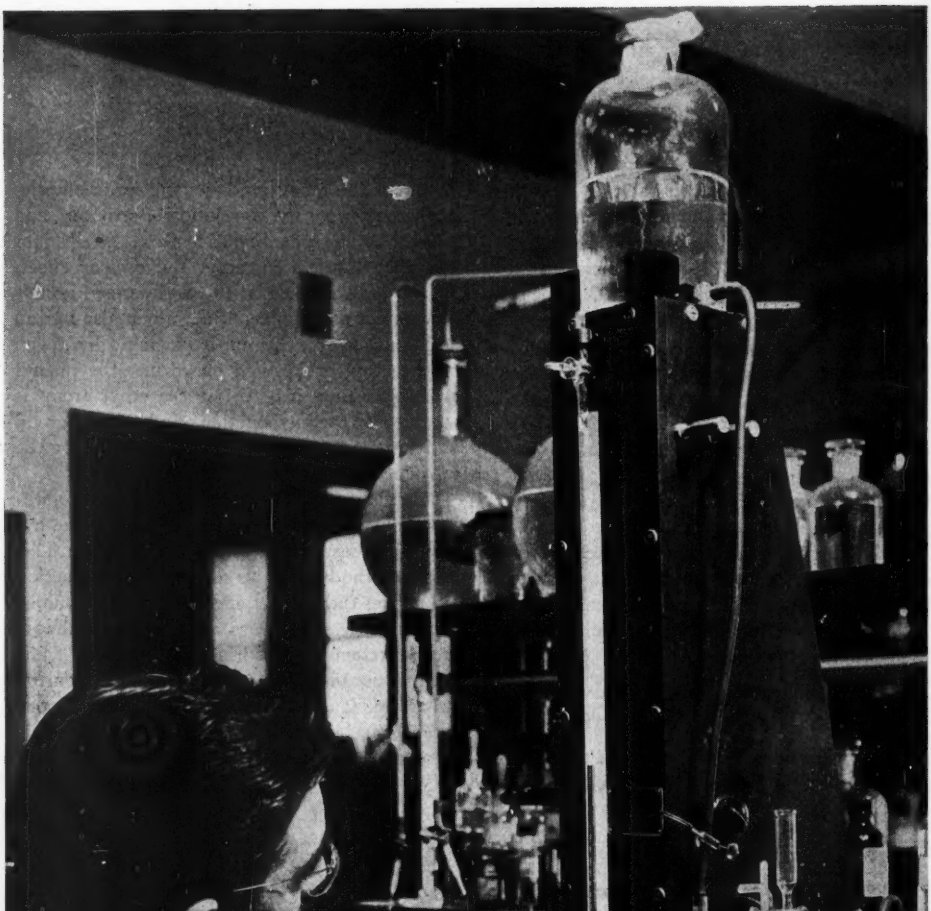


Many variations have been made and the products obtained have been carefully studied. A few of the many products will be briefly described showing the correlation of structure and effect. The introduction of hydroxyl groups into the phenyl group increases the pressor effect. This is most marked when two hydroxyl groups are present as in epinephrine which also has an additional hydroxyl group replacing a hydrogen of the ethyl group. In ephedrine the phenyl group is unsubstituted, but the ethyl group is modified by the introduction of a hydroxyl group and a methyl group, and the amine group by the introduction of a methyl group.

"Benzedrine,"[15] 1-phenyl-2-aminopropane, differs from phenylethyl amine in that a methyl group has been added to the ethyl group. This increases the central nervous stimulating action and makes the product effective on oral administration. Because it does not have the hydroxyl group present in ephedrine, it is volatile. The product used is a mixture of the *d* and *l* isomers. It has been found that *l*-benzedrine has good pressor action but little analeptic activity while the *d*-isomer has just the reverse effect. If one of

(*Continued on page 169*)

HORACE ABBOTT SHONLE, author of "The Organic Chemist," died on February 24, after a brief illness. His contributions in medicinal chemistry constitute a monument to a career of high purpose and of great service both to the public and to pharmaceutical science. It is a privilege for the Journal to present posthumously this discussion of research techniques that Mr. Shonle employed so effectively and brilliantly in his own work. He was director of the Division of Organic Chemistry at Eli Lilly & Co., where he had been on the research staff since 1919. Mr. Shonle was born in Tuscola, Ill., May 14, 1892. According to his own report, Mr. Shonle "carried out first chemistry experiments during high school days in the woodshed trying to distil road tar, with more than indifferent results (the building did not burn down)." It was the start of a career that gained him international recognition as an authority in his field. His first paper, bearing his name as co-author, was published in 1916 during undergraduate days at the University of Illinois. Following graduate work, he served in the Army with the Chemical Warfare Service, later with the Medical Corps, then joined the Lilly staff. Since that time he has been author and co-author of many papers and patents. Mr. Shonle had held several posts in the American Chemical Society and actively participated in a number of other professional and scientific organizations, including the American Pharmaceutical Association. Despite his devotion to pharmaceutical science, Mr. Shonle actively participated in church work, the Boy Scout movement, and civic projects. His untimely death is a great loss both to the public and to pharmacy.



The Biochemist

by

B. F. DAUBERT* and R. H. McCOY†

BIOCHEMISTRY may be described as that branch of science concerned primarily with the discovery and the determination of structure and function of chemical compounds that play a role in biological processes. Drugs may be defined as "all of those materials used as medicines." If these generalizations are accepted, one must conclude that the biochemist has played and will continue to play a major role in the development of many new drugs. Progress in this direction should continue as long as we learn more about the processes of metabolism and the factors that affect it.

The biochemist in his never-ending search for chemically explainable physiological processes has become quite adept at separating pure compounds from exceedingly complex mixtures. The separation of a protein, having enzyme or hormone properties, from a mixture of several kinds of proteins as well as fats, carbohydrates and other constituents of its complex milieu is often difficult. But the experience of biochemists in this type of endeavor has often proved of value in isolating and identifying substances having therapeutic merit.

During the process of separating active constituents from these complex mixtures a means of measuring the physiological activity must be developed. For example, in separating a vitamin, a solvent extraction, a precipitation or some other manipulation is employed that yields two or more fractions. All fractions must then be examined for physiological activity to determine whether an effective separation has occurred. These tests for activity often become the basis for bioassays in the control of the product. In this way, biochemists and pharmacologists frequently contribute much to each other's scientific field.

For a long time, biochemists have been interested in problems of metabolism. It is important to know the intermediate paths in converting the basic foodstuffs—carbohydrates, fats and proteins—to their end-products and to energy. To study these reactions, which are essentially enzymatic in nature, biochemists have developed a very important tool, the microrespirometer. This is a very ingenious instrument which permits easy measurements of the oxygen uptake and carbon dioxide output of very thin tissue slices, a small number of bacteria and in a few instances even single cells. By varying conditions, a well-trained biochemist can determine the effect of drugs on specific enzyme systems. Frequently such studies lead to knowledge relative to the mode of action of drugs and to possible disadvantageous side-actions and means of mitigating them.

In practice, rarely does any one group or individual develop a new drug. Ordinarily a new therapeutic agent will be the result of the combined efforts of several groups, such as biochemists, physiologists, pharmacologists and bacteriologists.

However, if one specific method or approach can be attributed to biochemistry, it is probably best represented by the following: First, observation of a physiological response to the administration of a naturally occurring substance; second, isolation of the active principle and its chemical identification; third, preparation of a suitable product for administration to human patients; and fourth, elucidation of the manner in which the substance produces the physiological response. Often, in the rush to take advantage of new research findings, the second step is temporarily omitted. Haste of this sort has occasionally resulted in the marketing of products with toxic effects.

In contrast with the method of the biochemist, the organic chemist may first synthesize a series of compounds and then study their physiological action. Thus, he may discover compounds that will be desirable as drugs. In addition, the organic chemist often studies the structure of naturally occurring compounds with known physiological actions. He then attempts to modify these natural products by synthesizing related compounds, in the hope that some of these may be potent remedial agents. Although substances of this type are not developed primarily by the

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biochemist, very often he cooperates in such a research program.

In this brief review we shall describe the story of a few products that have been developed mainly by the efforts of biochemists, to illustrate the types of procedure used.

Biochemical Method Applied to Insulin

Insulin provides a very good example of the use of the biochemical method. The original observation by Von Mering and Minkowski in 1889 that the removal of the pancreas from dogs led to a condition similar to human diabetes stimulated many investigators to study this relationship. Numerous experiments were necessary to demonstrate that a hormone produced by the pancreas was responsible for the specific effect upon carbohydrate metabolism. The isolation of the hormone, insulin, a protein, was complicated by the presence in pancreatic tissue of other proteins and a proteolytic enzyme that rapidly destroyed the insulin. In 1922 Banting and Best, together with Collip and MacLeod, succeeded in preparing a concentrated extract that was highly active in a diabetic animal and furthermore restored health in cases of diabetes in man.

Their first preparations were obtained by ligating the pancreatic duct in dogs, thus inducing degeneration of the pancreatic cells producing the proteolytic enzyme. After a few weeks the dogs were depancreatized and extracts of insulin prepared from these pancreases. Shortly thereafter, on the basis of the information obtained by a study of these extracts, methods were developed for preparing insulin directly from normal pancreatic tissues. Essentially this same procedure is in commercial use today for the removal of insulin from mammalian pancreases.

Insulin, being a protein, must be injected, because it is destroyed (i. e., digested) when taken by mouth. The original insulin solutions were absorbed rapidly and often brought about such rapid and marked lowering of blood sugar that convulsions occurred. For this reason, it was necessary to give two or three injections each day and to regulate very accurately the food intake of the patient.

To overcome this difficulty, many improvements have been made in the product to be injected. Most of these improvements are based upon the fact that insulin is an acidic protein and may be neutralized by more basic proteins or protein fragments. One of the most successful consists of the common "protamine zinc insulin," which generally brings about a gradual drop in blood sugar after four to six hours, and which exerts its activity for more than twenty-four hours. In addition, a "globin insulin with zinc" is available, which lowers blood sugar within two hours, and is active for twelve to fifteen hours.

Thus, a physiological action was observed, the active principle was isolated, and, finally, suitable preparations for administration to human patients were developed, all based upon the biochemist's knowledge of protein chemistry.

But this is not all of the story. Any drug can be more effectively used and prescribed if we know how it brings about its specific effects. The earlier concept, suggested by several investigators, stated that insulin was involved directly in the burning of carbohydrates and that in the complete absence of insulin the animal organism was unable to burn any sugar. Furthermore, all sugar, either fed or formed by the animal, would be excreted as such in the urine. Such theories are no longer tenable, for in the complete absence of insulin, large amounts of sugar can be burned.

Metabolic Studies

How, then, does insulin function? Until very recently only limited bits of evidence were available. About a year and a half ago Cori demonstrated a specific role of insulin. From studies of carbohydrate metabolism, we know that within the animal body glucose is converted by an enzyme, hexokinase, into a glucose phosphate, before it is either oxidized or converted into glycogen. The enzyme hexokinase is inhibited by a hormone or factor produced by the anterior pituitary. Cori demonstrated that the inhibitory effect of this factor is counteracted by insulin. Within the normal individual these two products serve as a check and balance system regulating the formation of this *reactive* form of glucose. In the presence of insulin, more glucose phosphate is available either for glycogen synthesis or for burning to provide energy. Thus, upon the basis of these biochemical findings, insulin can be more efficiently used and probably will be more extensively prescribed.

And there remain additional chapters yet to be written concerning insulin. If the exact chemical nature of a physiologically active natural product is known, it is possible that a more potent product can be prepared synthetically. Insulin as a protein probably could not be synthesized as such in the laboratory even if we knew

its exact structure. To date, eleven amino acids have been isolated from crystalline insulin. An equal number of free amino groups (i. e., amino groups not combined in peptide linkage) of glycine, phenylalanine and the epsilon-amino group of lysine have been demonstrated to be present in the insulin molecule. Whether additional information of this type—obtainable by the use of some of the new procedures developed for the study of protein structure—may reveal a unique chemical grouping responsible for the action of insulin is problematical. If such a unique structure can be identified within the insulin molecule, then the possibility of synthesizing this grouping and using it for the treatment of diabetes is greatly enhanced.

Dr. Best, in commenting upon the present insulin picture, said, "If the present rate of increased use of insulin continues, all the available pancreas in the world will be utilized for insulin production in the not distant future." This demand for additional quantities of insulin, or at least a physiologically active product, may help to bring about the final clarification of the specific chemical groupings responsible for the action of insulin.

Research on Vitamins

The production of vitamins serves also to illustrate the methods of the biochemist. The original observations reported by Eijkman demonstrated that the diet of human beings suffering from beriberi when fed to pigeons led to a similar condition. Rice polishings added to the diet of the pigeons alleviated their symptoms. Eijkman succeeded in producing extracts that were effective under some conditions for curing or alleviating the beriberi of human patients. Williams began studies of these extracts shortly after 1900 and within a few years had obtained a highly potent product. However, despite almost continuous work by many investigators, it was not until 1926 that a pure crystalline compound was obtained by Jansen and Donath—the first pure vitamin, thiamine. It required ten years of additional work before Williams succeeded in identifying and synthesizing this compound, after which studies were inaugurated to determine the effect of thiamine on intermediary metabolism. Today synthetic thiamine is available, both for the treatment and the prevention of beri-beri.

Again, the story records the observation of a natural product that brought about a marked physiological response, the isolation and chemical identification of this product, and finally the development of a material suitable for human consumption and the determination of its mode of action.

Microbiological Assay

Another interesting chapter in the development of new drugs by the biochemist is dependent upon the use of a new procedure, that of microbiological assays. The biochemist needed quantitative methods suitable for extremely small amounts of certain materials, but he was unable in many cases to develop suitable chemical procedures for such analyses. Within the last five years the biochemist, together with the bacteriologist, has developed microbiological procedures for determining vitamins, amino acids and a number of other products.

These techniques permit assays on minute samples and in turn help to clarify the role of a number of products in metabolism. In general, a suitable microorganism is chosen as the assay organism, and it is inoculated into a medium complete in substances necessary for optimal growth *except* the substance being assayed. The substance being assayed is added in graded amounts to vessels containing the inoculum. After the requisite incubation period, the effect of the "unknown" on the growth of the microorganisms is determined by the turbidity of the medium or by the measurement of some metabolic product, such as lactic acid. In this way minute amounts (often as little as a millionth of a gram) of an essential vitamin, amino acid or other substance of physiological importance may be determined with remarkable accuracy.

One example will serve to demonstrate the value of this new technique. In 1938 Stokstad and Manning observed that chicks grew better on a diet of natural foods than on a similar diet in which the yeast was replaced by purified vitamins. Under similar conditions Hogan and Parrott in 1939 found an anemia in chicks on a purified diet. Snell and Peterson reported a crude preparation of an unknown factor essential for the growth of *Lactobacillus casei E.* The general properties of these three crude preparations were similar, and biological tests suggested that only one active ingredient was involved. On this assumption, the microbiological assay procedure served as the major test during the isolation of the unknown factor, this procedure being much more rapid and consuming much less material than the chick assay method. Identification was completed, and synthesis of folic acid was announced in July, 1945, only seven

years after the first recorded evidence for this dietary factor.

Some investigators feel that without this very sensitive microbiological test, the isolation of folic acid would have been an impossible task. Since the compound is effective in the prevention of an anemia in the chick, it was tested on human patients having various types of anemia. In a number of these cases the patients showed a prompt reticulocyte response. This suggested that folic acid deficiency may occur in the human. Certainly folic acid is another drug in the sense that it is an effective therapeutic agent for a considerable number of chronic anemias that do not respond to the usual type of therapy with iron and liver. Microbiological methods have served as useful tools in several other examples of the isolation of physiologically active compounds from natural materials and thus have helped the biochemist in the development of new drugs.

The rapid development of the steroid hormones as biochemical entities and potential drugs began in 1929 when Doisy and Butenandt isolated estrone from human pregnancy urine. Since that date, there have been developed both naturally occurring and synthetic substances having androgenic, estrogenic, progestational and adrenocortical effects. These products have received wide acceptance in clinical medicine.

For example, certain phases of Addison's disease, one of the long-unsolved problems for the clinician, now can be treated by adrenal cortical hormone therapy with reasonable success. Here again is an example of a product developed in the laboratory for clinical use which represents a new addition to the armamentarium of drugs.

Antibiotic Concepts

The entire concept of the development of *antibiotics* (against life)—substances that interfere with the normal growth of pathogenic organisms—has been the result largely of the interest of the biochemist in factors affecting the metabolism of living organisms. The development, particularly, of mold-produced antibiotics, of which penicillin is a typical example, has been a fascinating one.

The story of penicillin began with Fleming's initial observation in 1929 that on plate cultures of Staphylococcus organisms contaminated by mold colonies there invariably resulted a transparent area surrounding the mold. Fleming suggested that this unusual phenomenon was the result of the production by the mold of a bacteriolytic substance which diffused into the media on which the Staphylococcus organism was grown. Further work on filtrates obtained from the mold grown on nutrient broth verified his conclusions. Although Fleming thought that the parent mold was a strain of *Penicillium rubrum*, it was later identified more exactly by Thom as *Penicillium notatum*. Here is testimony of the production by a common mold during its normal metabolic processes of a substance having physiological activity, particularly against certain types of bacterial organisms. Thus, the first step of the biochemical method in the development of a new drug in this case was taken by Fleming, a British bacteriologist.

Studies on Penicillin

Cooperative investigations by the biochemist in terms of providing better nutrition for the mold and better methods for extraction of the antibiotic, as well as the development of methods for assaying its inhibitory powers, resulted in rapid progress toward its isolation, increase in yield and the subsequent assessment of its therapeutic value. When the existence of penicillin K, F and other penicillins was discovered, biochemists were particularly helpful in finding precursors that could be added to the media in order to assure high yields of penicillin G or any other specific penicillin.

The Herculean cooperative research efforts during the war years of bacteriologists, biochemists, organic chemists, physiologists, pharmacologists and others have culminated in the isolation of a chemically pure compound. The structure determination of penicillin, and eventually a commercially practical synthesis, is the next logical step in order that man in the future will not have to depend on the whims of a common mold for this important antibiotic. The research on its chemical moiety has been prodigious, and has occupied the attention of many organic and biochemical research groups the past several years.

Although the exact chemical structure of penicillin has eluded their best efforts and is still unknown, du Vigneaud in November, 1946, reported the *laboratory* synthesis of a penicillin. It is only a matter of time until the cooperative efforts of the organic chemist and the biochemist will lead to the establishment of its exact nature and subsequently its total synthesis. Undoubtedly, the structure of several other antibiotic substances will be determined in the near future and also become available as synthetic products.

The determination of the mode of action and

the method of detoxification of a drug is not only of great value in determining the limit of usefulness of the specific drug in question, but it often leads to the discovery of other drugs. Organic chemists have given a great deal of attention to synthetic compounds having a structure similar to epinephrine, as described elsewhere in this issue. A biochemical study of the manner in which these amines are destroyed in the tissues can sometimes be correlated with the difference in intensity and duration of action. If the chemist can know what specific groups may be changed on such compounds to make them inaccessible to certain enzyme systems that destroy them in the body, the duration of action may be prolonged.

Enzyme Reactions

For some time it has been recognized that allergy and related phenomena are similar to the reactions produced by histamine. Consequently, the biochemistry and pharmacology of histamine reactions have been studied at great length. Biochemists, studying the effect of structural changes on enzyme systems, discovered that compounds having certain structural features in common with a substance easily destroyed by an enzyme frequently can be made to combine with the enzyme and inhibit its action.

Taking the clue from enzyme inhibition studies, it was suggested that organic chemists could produce compounds having sufficient structural similarity to histamine to unite with the same portions of the cell that unite with histamine. Thus histamine would be prevented from reacting and at the same time these compounds would themselves be physiologically inert. In this way any allergic phenomena due to aberrant histamine metabolism would be prevented. These biochemical concepts led to the development and introduction of such drugs as benadryl and pyribenzamine.

It is difficult to draw a hard and fast line between the efforts of the biochemist and those of the bacteriologist, physiologist, pharmacologist and the clinician in the continuing search for new remedial agents. The foregoing brief discussion, however, has served to emphasize what may be defined conveniently as the biochemical method. This method has been used by investigators in all fields.

Biological chemistry has made possible the study of the functions and the influence of the endocrine glands on metabolism, the digestion and absorption of food, the processes by which the animal body disposes of its waste matter, and the methods by which it immunizes itself against disease. A great storehouse of information has thus been accumulated to give us bases for the development of an entirely new group of drugs.

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The Bacteriologist

by

LOUIS GERSHENFELD*

SINCE the basic researches of Pasteur less than a century ago, bacteriology has provided a steadily increasing impetus to man's conquest of infectious diseases. As the basic science of medical bacteriology developed, bacteriologic techniques became the tools of the microbiologist, parasitologist, immunologist and other "specialized bacteriologists." Indeed, they are today an aid to investigators with primary interests in entirely separate fields.

Contributions to the development of new drugs, which we shall discuss, may be made by the bacteriologist as such, or by any of the specialists working in the broad field of bacteriology. The bacteriologist is an important member of the modern research team that provides a coordinated attack on a therapeutic problem from various points of approach. In the field of chemotherapy his work is an indispensable link in the chain of investigations. But it is in the field of biologicals that the bacteriologist becomes primarily responsible for the advent of important therapeutic agents—products that may be important in diagnosis and prevention as well as in treatment.

Biologicals

Biologicals have been deemed of such importance by the Federal government that their production and distribution in interstate commerce is subject to the provisions of a special act of Congress. The biologics law, antedating even the 1906 Food and Drug Act, is administered by the U. S. Public Health Service and is discussed elsewhere in this issue. Biologicals for veterinary use, marketed through interstate commerce, are licensed by the Bureau of Animal Industry of the U. S. Department of Agriculture.

Development and production of biological products[1] may embrace any of the following types of agents used for the prophylaxis or treatment of disease:

1. Bacterial vaccines (which are known also as bacterial antigens, bacterins or opsonogens).
2. Antimicrobic sera (known also as antibacterial or therapeutic or immune serums, or antiserums).
3. Sensitized bacterial vaccines (serobacterins).
4. Antitoxins (antitoxic sera).
5. Modified or attenuated viruses (virus vaccines).
6. Immunizing toxins.
7. Toxoids or modified toxins.
8. T-A mixture.
9. Tuberculins.
10. Phylacogens and bacterial culture filtrates.
11. Aggressins (natural tissue fluids from artificially infected animals).
12. Immunogens (ectoantigens).
13. Extracts or allergens (animal, bacterial, or vegetable extracts).
14. Proteins for specific and nonspecific protein therapy.
15. Diagnostic and biological reagents.
16. Antivenin.
17. Normal serum and citrated plasma.

Bacteriological research leading to commercial production of biological products starts when attempts are made to determine the causative agent or agents of a particular disease. Is the etiological factor a bacterium, a virus, a yeast, mold, or one of the rickettsia, protozoa, or higher forms of life?

It is not always possible to be certain that organisms which the bacteriologist finds in blood, pus, urine, or in a disease lesion represent the cause of the disease under observation. To prove that the organisms found are actually the causative agents requires painstaking study. Detailed and careful investigations must be carried out to demonstrate conclusively the connection between the organisms and the particular disease.

The first exact methods applied to the study of the etiology of disease were introduced by Robert Koch when he established the pure culture technique. The evidence required by Koch's

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four postulates, given below, is still of great value today in establishing the etiologic factor:

1. The specific organism should be constantly present and associated with the disease observed.
2. Pure cultures should be isolated from the pathologic material.
3. These pure cultures inoculated into suitable healthy animals should produce the same pathologic conditions as originally observed.
4. The organism should be recovered in pure culture from the experimental animal to which the disease was given.

Koch's postulates are based on an ability to obtain pure cultures of an organism that will reproduce the disease when inoculated into suitable animals. It is readily apparent that this concept represents important research problems of great magnitude. For instance, viruses and rickettsia will grow only in living susceptible cells, and they are often specifically adapted to one or a few animal or plant hosts. A task for the research worker is to find the suitable host and the specific living susceptible cells or tissue in the host. The nutritive requirements and conditions for optimum growth vary for different bacteria. If the suspected etiological factor is a bacterium, then it is essential to make available a suitable nutrient culture medium and favorable conditions for optimum growth.

In any such research investigation, the bacteriologist may find that the usual methods of systematic study are inadequate. He then may be compelled to devise new methods of procedure for identification—perhaps a new staining technique, a new biochemical test, or other means of investigative observation.

In his studies he will attempt to learn all characteristics peculiar to a particular etiologic factor. If it is a bacterium, he will note whether toxin is present and the kind of toxin produced. He then becomes concerned with possible methods of treating and preventing the disease under study. In one instance an effective agent may be found in the field of chemotherapy; in another it may be found in biological therapy.

Research aimed at obtaining chemotherapeutic agents will be detailed elsewhere in this issue. Research on biologicals, in which we are particularly interested here, is aimed at inducing artificially acquired immunity (i.e., marked resistance) to a particular pathogenic organism.

A product producing the desired immunity reaction may contain (1) microorganisms of an infectious disease, (2) a complex substance composed of the products of growth of microorganisms, or (3) an animal product containing substances antagonistic to microorganisms or their products.

Antigens (e.g., bacterial and viral vaccines, toxins and toxoids) are employed with the hope of producing an effective active immunity, stimulating production of specific antibodies within the patient. Serums and antitoxins, containing antibodies from the blood of immunized animals, are administered to the patient to antagonize directly the invading bacteria and viruses, representing a passive immunity.

A biological is much more specific in its action than a chemical agent, since it protects only against a particular pathogen (and in a very few instances against closely related organisms). We have yet to discover any one agent that, either by natural or artificial means, will confer general immunity against all known pathogenic organisms.

Antigenic Structure

In studying the possibility of preparing vaccines, serums, or other biological products, the bacteriologist may be led into an investigation concerning the antigenic structure of the organism and, in particular, the nature of components possessing the property of stimulating the tissues of living animals or humans to produce specific antibodies. Some strains of a specific organism may possess all characteristics of the species, and yet be weak antigens. Only strains that are good antigens are used to produce biological products.

Studies of antigenic structure also may result in the development of various biological or immunological tests that will be found useful as aids in the diagnosis and prognosis of suspected cases of the particular disease, or in determining if an immunity prevails.

A preparation of the antigen or antibodies that will produce the required immunity reaction in the animal body is only the first step in a long series of investigations. The method of administration and dosage must be studied in animals. Untoward reactions due to foreign protein frequently present a difficult problem in the field of biologicals. This danger may sometimes be minimized by methods of purification and concentration, by modifying a serum through the action of enzymes, or by using serum only from a particular species of animal. Tests for potency and for identity must be developed, although neither may be achieved with the degree

of accuracy possible in the field of chemotherapy. Additional investigations will develop other practical methods of concentrating and purifying the immunizing preparation. Safety of the biological under normal conditions of use must be assured. And finally come the controlled clinical trials.

Gathering Data on Proposed Biological

When a biological product appears ready for marketing, application must be made to the U. S. Public Health Service, or in the case of veterinary products to the Bureau of Animal Industry. The work of the bacteriologist may be further elucidated by describing some of the data supplied with a license application for a product such as a bacterial vaccine, even when the producer already holds an establishment license.

In describing the composition of the product one indicates the organism or organisms employed; the proportion, source, and strain of each organism; the methods of identifying each organism and the frequency with which these methods are to be applied.

The bacteriologist must be able to state the purity, virulence, and antigenicity of the cultures, and how these characteristics are determined and maintained.

With regard to the media, one notes the composition, reaction, and method of preparation and sterilization—both for propagating seed cultures and production cultures.

Production procedure is detailed step by step: the kind of flasks used for growing cultures, preparation of suspensions for seeding, techniques of inoculating the seed medium and production medium, and temperature and period of incubating each organism. Then comes the processing subsequent to incubation. Are the bacteria killed or attenuated by heat, germicide or by other means, and how is this accomplished? How is the product standardized, and how many bacteria are present per cc. or per individual dose? The potency test, if one is applicable, or other means of determining in animals the efficacy of the product, as well as other tests for purity, safety, etc., are also included in an adequate report on the proposed biological.

One must also have data on the containers to be used for the final product, the method of filling, storage requirements and dating period, on dosage and on clinical studies.

In the manufacture of biologicals where animals are used in production—such as for antisera, antitoxins, virus vaccines, and aggressins—the bacteriologist must have developed adequate data such as described above for a bacterial vaccine with appropriate modifications. When animals are involved, a report demonstrating adequate developmental work for a product license will also include detailed information on the animal species used, age, health, quarantine period, and other characteristics determined. In a step-by-step description of production involving animals there will be, in addition, information on such factors as the method, number, and sites of inoculation; the character and dose of the antigen; time required for immunization or hyperimmunization; and (if bleedings are conducted) the method of bleedings, number of preliminary bleedings, volume of blood collected, and elapsed time between the last injection and the first bleeding, and between subsequent bleedings.

The data briefly mentioned above—which are among those reported in applying for a Federal product license—indicate the scope of procedures about which the bacteriologist must have adequate knowledge before a biological may be considered for general clinical use.

It becomes clear that the role of the bacteriologist is a responsible one. The research bacteriologist concerned with determining the etiology of diseases and developing biologicals for medical use must be especially competent and well qualified in his field. The responsibilities of key personnel in a manufacturing establishment are no less important, and competent bacteriologists are charged with the supervision of all important details.

Like other specialists in the broad field of medicine and pharmacy, the bacteriologist cannot achieve his objectives alone, and he relies heavily upon the chemist, the pharmacologist, and the clinician to provide essential links in the chain of investigations necessary to make a safe and effective biological available to the patient.

Anti-Infectives

In chemotherapy a new product with therapeutic possibilities will usually originate in a field other than bacteriology—antibiotics being a particularly notable exception—although the bacteriologist, mycologist, or parasitologist usually will be a member of a research team, to evaluate the effectiveness of a drug against pathogenic organisms. Drugs used in the chemotherapy of infections fall into two large groups: the locally acting antiseptics, and the anti-infectives for internal administration. No-

table additions have been made to both groups within the past few years, particularly since the advent of the sulfonamides.

Evaluation of Antiseptics

Local antiseptics have continued to hold the interest of a number of research workers, and their evaluation presents special problems that the bacteriologist is called upon to solve.

Under the Federal Food, Drug and Cosmetic Act a drug labeled as an antiseptic is expected to be germicidal, except when intended for inhibitory use in a manner involving prolonged contact with the body. In other words, preparations such as eyewashes, douches, mouthwashes, gargles and nose drops may be labeled antiseptic only if they will destroy microorganisms, when used as directed, within the short time they are in contact (usually not more than a few minutes and frequently only a fraction of a minute). Ointments, dressings and dusting powders, which remain in contact for a long period of time (usually several hours or more), may properly be designated antiseptics if their action only inhibits the growth of microorganisms.

Antiseptics vary markedly in physical and chemical characteristics, mechanism of action, mode of application and therapeutic use. With so many variables, the evaluation of a new compound and an attempt to appraise its merits and demerits represent a complex and difficult task. Yet, it must be done. The Food and Drug Administration may be concerned primarily with the safety, low tissue toxicity, and effective bactericidal activity under the intended conditions of application. But the manufacturer will also be concerned with other factors such as ease of application, stability, penetrating power, effects of different temperatures, esthetic factors, and freedom from damaging effects to linen, instruments, or other material.

Forty years have passed since Rideal and Walker introduced phenol as a basis of comparing and standardizing disinfectants. Research on the evaluation of antiseptic compounds went forward during that period but gained impetus with the passage of the 1938 Food, Drug and Cosmetic Act. Yet today, in gathering laboratory data on the efficacy of an antiseptic, one must recognize that there is not a universal, single test applicable under all conditions.

FDA methods have been offered as useful *in vitro* tests but not as universally applicable "standard" or "approved" procedures. The bacteriologist will perform an array of different kinds of tests better to substantiate the claims to be made for a new drug as an antiseptic. When an antiseptic shows constantly satisfactory effectiveness by many different methods one can then conclude that it deserves a high rating of usefulness as a bactericidal agent.[2] Data differentiating bacteriostatic efficiency from bactericidal efficiency may also be significant. *In vitro* tests are supplemented wherever applicable by *in vivo* techniques. In all instances laboratory data should be obtained under conditions paralleling as closely as possible those found in actual practice. Efficacy under conditions of use (as recommended in labeling) is, in the final analysis, the important criterion.

The role of the bacteriologist in evaluating a new drug as an antiseptic can be illustrated best by considering the problems he encounters and the tests he must perform on a new product for use on the skin to treat or prevent infection.

The phenol coefficient technique[3] may be used as a starting point, and is employed as follows: Under aseptic conditions, 0.5 cc. of a bacterial culture is added at designated intervals to 5 cc. of various dilutions of the preparation being tested. These mixtures are kept in a water bath at body temperature (37° C.). At 5, 10, and 15 minute intervals, standard 4 mm. loopfuls from each of the inoculated (medication) mixtures are transferred separately to tubes containing 10 cc. standard FDA broth. After incubation at 37° C. for 48 hours the subculture tubes are examined macroscopically. If the subculture tubes (transplants) appear the same as they did before inoculation (i.e., clear), it indicates a lack of growth and is interpreted to mean that the dilution of antiseptic used killed the bacteria. Turbidity or cloudiness in the subcultures indicates growth and is interpreted to mean that the antiseptic dilution failed to kill or prevent growth.

If the bacteriologist suspects that the cloudiness is actually not due to growth of the test organism, he will examine the subculture microscopically and, if necessary, proceed to other methods of differentiation. If desired, the results of this test may be compared with dilutions of phenol examined under identical conditions. By computation this comparison may be expressed in terms of the phenol coefficient, a numerical figure that indicates how much greater, or less, is the bactericidal efficiency of a particular disinfectant as compared with phenol.

The effectiveness of an antiseptic may be altered in the presence of proteins or other organic matter. The above *in vitro* test is fre-

quently conducted in the presence of organic matter by adding serum (human, horse, or other animal) before addition of the broth culture of the test organism. Some workers employ organic matter other than serum.

Absence of bacterial growth in the above transplant tubes may be due to either bactericidal action (actual killing effect) or bacteriostatic action (merely preventing growth and development). Transplants from subculture tubes (containing the highest dilution of the antiseptic) will reveal whether or not the action is merely that of a bacteriostatic agent, for the subsequent dilution nullifies a purely bacteriostatic action. It is also possible to determine this by making the initial transfers into 100 or 200 cc. of medium. This presents a laboratory technique which is cumbersome, however, and which is not practical as a routine procedure. Much research has been conducted by bacteriologists to find substances that can be incorporated into culture media which would not affect bacterial growth and which would neutralize any bacteriostatic activity of the medicament.[4,5,6]

At times it may be necessary to determine the virucidal properties of a new substance. Techniques similar to that used for testing bactericides can be employed. An emulsion of the virus-containing material can be prepared in broth. Inasmuch as viruses require suitable living cells in a host for growth and development, susceptible animals are inoculated. In lieu of subcultures or animals, the chorio-allantoic membrane of the 10-day-old chick embryo is used, and the incubated eggs are inoculated. In these instances, failure to infect would indicate a virucidal effect at the dilution of chemical employed.

As in the case of testing virucides, a uniform method of testing substances (new and old) for their fungicidal effect is also available. Emmons,[7] Klarmann,[8] and others, have suggested modifications of the FDA technique as well as other techniques, using as the test organism various species of trichophyton, monilia, etc.

It may even be necessary for the bacteriologist to develop new procedures, in addition to modifications of the above tests, if the bactericidal, fungicidal, or virucidal action of a new compound is to be evaluated satisfactorily.

The wet filter paper method[3] may be more satisfactory for testing new substances that are not completely soluble or miscible with water, or for substances that are employed in weak dilution. The dry filter paper method is used in testing fumigants and oils that are employed in the absence of moisture.

The agar plate method[3] supplies data concerning the bacteriostatic properties of substances, other than liquids, that are used in contact with the body in the absence of serous fluids. These include ointments, creams, plasters, adhesive tape, dusting powders, etc. A variation of this test, the agar cup plate method,[3] is used if the product is liquid at the temperature of the test. Some workers regard these plate methods as supplying information concerning the penetrative power of the medicament.

More recently various toxicity tests have been introduced as aids in determining the toxic effects of antiseptics on different kinds of living tissue, as contrasted with their lethal effect on microorganisms. All of the laboratory tests performed should be interpretable in terms of practical use. It is obvious that laboratory

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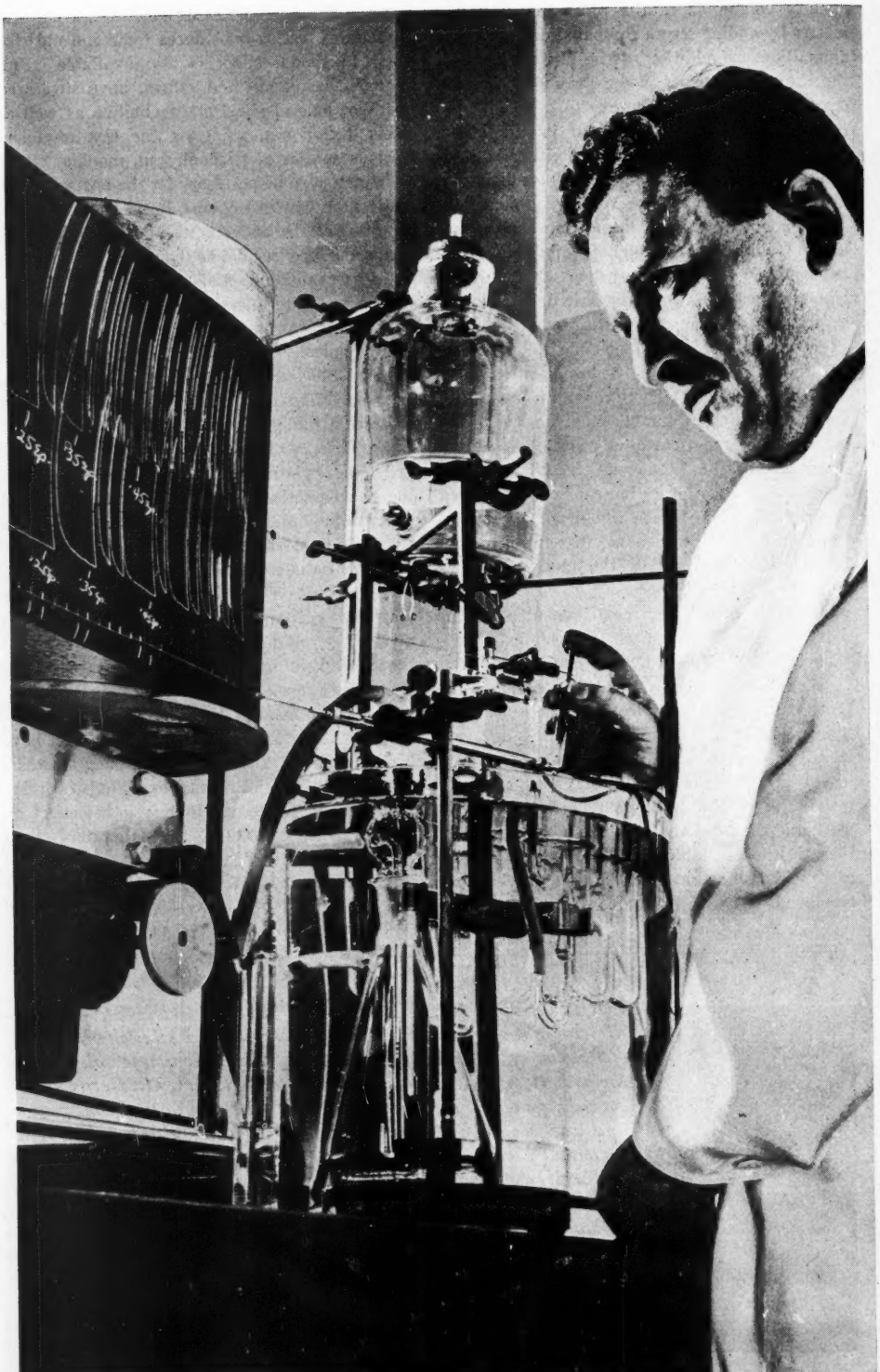
LOUIS GERSHENFELD, author of "The Bacteriologist," has been director of the department of bacteriology at the Philadelphia College of Pharmacy and Science since 1917. Widely known for his work in the bacteriological sciences as applied to pharmacy, Dr. Gershenfeld's contributions to the literature include four books, numerous papers, and work on the U. S. Dispensatory as associate editor and on Remington's Practice of Pharmacy and Merck's Index as collaborator. In the field of official standards, Dr. Gershenfeld has served on both U. S. P. and N. F. committees concerned with bacteriology. He is a member of the executive and finance committees of the National Biological Stain Commission, and former secretary of the Commission. Other posts have included the chairmanship of bacteriology groups in the National Council on Pharmaceutical Research and the Pharmaceutical Syllabus Committee. Pharmaceutical industry and government agencies have frequently sought his services as a consultant.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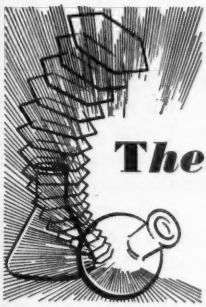

The Pharmacologist

by

JOHN C. KRANTZ, JR.*

PHARMACOLOGY, in its broadest sense, embraces all of the information extant on drugs. Thus its scope might include the preparation, synthesis, action and therapeutic application of substances used as drugs. In its restricted meaning, the science of pharmacology concerns the response of living cells to chemical stimuli. Even this restricted field is far-reaching in its scope and includes insecticides, plant poisons, animal poisons, hormones, vitamins and therapeutic agents as they act upon living cells. The physician and pharmacist, however, are primarily concerned with pharmacodynamics or the action of substances used as drugs on tissues and systems devoid of disease and with pharmacotherapy which involves the same type of action in the presence of disease.

Although pharmacology is the latest of the medical sciences to take its place in the curricula of schools of medicine and pharmacy its record of achievement in research and the knowledge it imparts to the student has made its position enviable. Pharmacology attempts to unravel the so-called mysteries of therapeutics. Pharmacology makes an effort to augment the physician's armamentarium with more useful therapeutic agents. Pharmacology by its efforts in biological assay has brought more dependable therapeutic agents to the pharmacy and hence to the bedside of the sick. In addition the pharmacologist with his formidable ally, the pharmaceutical chemist, has endeavored to correlate the fascinating and fertile relationship that exists between chemical constitution and the response of living cells to drugs. The purpose of this discussion will be confined to the role played by the pharmacologist in the developing of new drugs.

In the development of new drugs, the pharmacologist generally works as a member of a team. Many times he is the leader of the group of investigators or at least plays a prominent part in mapping out the grand strategy of the group. The team should have as its members, organic chemists, a bacteriologist, pathologist, biological chemist, if possible a physical chemist and also a close liaison with skilled therapeutists. Let us consider the operation of such a scientific team.

At the very outset one can state without hesitation that in man's conquest of disease all fields are still wide open. They are open in some instances, such as cancer, for the coming of the first therapeutic agent. They are open in other instances, such as malaria, for improvement in the therapeutic agents available. Such improvement may be forthcoming along any one of the following lines: lesser degree of toxicity, greater efficacy with a smaller dose, ease of synthesis which means reduction of cost to the patient and, finally, diminished untoward effects. As a rule the research group selects one very limited field of investigation. In doing this the group leader exhibits wisdom. One must realize that investigations of this character, which are exhaustive and expensive, represent large investments of talent and funds over long time periods and to diffuse one's efforts over too large an area generally results in disappointment and failure.

Therefore, an area of investigation is chosen, perhaps because it represents a special skill of the group leader, or the leader may respond to the urgency of a human need, such as cancer research or a national emergency such as the wartime malaria investigation. On the other hand, the dominating influence of the group may be less altruistic and rest entirely upon the pecuniary returns that will result from the sale of an agent that meets a definite therapeutic need. Without considering other possible motivating forces, which may direct the operations and destinies of a research team, let us consider a specific problem.

A new anesthetic of a volatile character is desirable. The disadvantages and drawbacks of the most generally used agents, such as ether and cyclopropane, are given consideration. The mechanism of how these agents produce the hiatus in consciousness, known as surgical anesthesia, must be investigated. Data available reveal that the generally used volatile anesthetics are characterized by having a high oil/water coefficient. Evidence indicates that they inactivate one of the enzyme systems present in the

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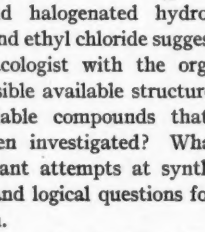
brain, namely the cytochrome reductase system and thus diminish the oxygen uptake and carbon dioxide output of brain tissue. This, in a measure at least, is responsible for the reversible pharmacological syndrome of surgical anesthesia.

With information of this character in mind, the types of molecules to be synthesized are considered. Low boiling ethers like ethyl ether, gaseous hydrocarbons like ethylene and cyclopropane, and halogenated hydrocarbons like chloroform and ethyl chloride suggest themselves. The pharmacologist with the organic chemist consider possible available structures. Have all of the available compounds that have been prepared been investigated? What new compounds warrant attempts at synthesis? These are natural and logical questions for the group's consideration.

Let us suppose that the difficulties in synthesis have been overcome and after much effort a molecule such as cyclopropyl vinyl ether is made. One notes from the structure that it contains the cyclopropyl group of cyclopropane, the double bond of ethylene, and carbon through oxygen bond of diethyl ether, accordingly:



Before the pharmacologist begins his work the chemist must be certain (i. e., sufficiently certain for human purposes) that the compound is the substance represented by its chemical formula. In addition, the chemist must be certain that the compound is pure and free as far as possible from contaminating impurities. The reasons for these requirements are perfectly obvious and to disregard them leads to misinformation, untold difficulties and wasteful expenditure of time.

Having been assured of the identity and purity of the compound in question, the pharmacologist must have it in sufficient quantity for complete study. There is nothing more devastating to a pharmacological study than a miserly supply of the agent under investigation.

This compound was synthesized primarily for anesthetic purposes, so let us try that first; but on what species? Anesthetics show a wide species variation. Therefore it will be prudent to select a species close to man, say the *macacus rhesus* monkey.

A volatile liquid anesthetic should be administered like ether. So, using the open drop method, anesthesia is begun. The induction is smooth and rapid. Respiration and heart rate seem to be little affected. The animal does not respond to pain stimuli. The musculature of the abdomen appears to be relaxed. The anesthetic cone is removed. The animal awakens slowly. There is no marked struggle. The equilibrium sense of the monkey is gradually restored. The mucous membranes of the eyes and nose do not appear irritated. The animal appears to be in good condition the next day. The first hurdle is past. There is promise in the compound; it is an anesthetic, or more strictly speaking it has exhibited anesthetic properties in one monkey.

The experiment is repeated several times on different monkeys. Pharmacologically the dog frequently exhibits responses to drugs closer to man than any other species. Anesthesias are therefore conducted on several dogs. As these animals are more readily available and less expensive, extensive experiments are carried out on this species. Blood pressure studies are conducted on the dog during the various stages of anesthesia. Is the blood pressure altered? Does the heart continue to beat when the animal is brought to respiratory arrest? These are important pharmacological questions and have special clinical significance.

Let us suppose that this new ether did not appreciably alter the blood pressure and further did not cause cardiac stoppage at respiratory arrest. Next, what about cardiac rhythmicity? Several anesthesias are conducted on dogs and electrocardiographic records are made. These will reveal the influence of the anesthetic syndrome on the cardiac regularity electric potential and on the auricular and ventricular activities, respectively. As certain anesthetic agents, such as cyclopropane, have a tendency to produce cardiac irregularities, this test is of paramount importance. It is best to include another species in the tests such as the *macacus rhesus* monkey.

In the use of an anesthetic, the amounts required to induce anesthesia and to produce respiratory arrest are important. The greater the difference between these values, the greater the margin of safety the agent exhibits. This is referred to as the anesthetic index. It is measured quite well on dogs. Under quantitative experimental conditions, the volume of the ether per kilogram required to induce anesthesia is determined and, further, that volume required to produce respiratory arrest is ascertained.

These values vary greatly for different animals and a large series must be run. The data must be subjected to statistical analysis to determine its significance. Suppose we find 0.4 cc./Kg. re-

quired for induction and 1.6 cc./Kg. for respiratory arrest. The anesthetic index is then 1.6/0.4 = 4. This is high and bespeaks a high potency and wide margin of safety. It reveals that during anesthesia only small concentrations of the ether will be circulating in the blood.

Certain anesthetics are definitely cardiotoxic. Chloroform is the chief offender in this respect. One can perfuse through the frog's heart *in situ* a Ringer's solution in which either chloroform or ether is dissolved. Ether will demonstrate itself to be about one-thirtieth as toxic to the heart as chloroform. With these two well-known anesthetics as yardsticks, by comparative tests the relative cardiac toxicity of cyclopropyl vinyl ether can be determined. In other words if this agent requires ten to fifteen times the concentration required by chloroform to show cardiac inhibition, the toxicity of the new ether to the myocardium lies about midway between ether and chloroform.

All of these tests look promising but much more must be done. Repetitious anesthesias of long duration on monkeys and dogs are observed and then come biopsies of liver and kidney tissues for pathologic study. Functional liver and kidney tests are also important. The concentration of nonprotein nitrogen in the blood after anesthesia is revealing with regard to kidney toxicity. Delayed anesthetic deaths in large populations of mice and rats upon repeated and prolonged anesthesias are significant. The effect on the clotting time of blood must be determined. The concentration that will produce hemolysis must also be determined. The compatibility of anesthesia with the new agent and other depressant drugs such as the barbiturates, morphine, nitrous oxide and cyclopropane must be determined.

The fate of the agent in the body is of utmost importance. Is it excreted unchanged? If not what are the metabolites formed and how are they excreted? An analytical method for blood concentrations is frequently a most difficult problem; yet it is so important in determining the comparative potency and the excretion time.

When all of these tests have been conducted and not any interdict the use of the agent in man and, further, one has had the opportunity during these studies to see some two hundred or more anesthesias in several species of animals, one is ready for human trial.

Even with all of these favorable animal data behind one, the administration of a new anesthetic agent for the first time to a human being is a hazardous procedure. The volunteer should be made mindful of the risk. All of the apparatus of resuscitation and stimulating drugs should be immediately available. Then with the highest degree of skill in the art of anesthesia, the agent is administered. All possible danger signals are watched for. If the anesthesia appears to be safe it is then ready for careful and judicious trial in the clinic.

The anesthesiologist selected for the tests should be one well experienced with all types of volatile anesthetic agents. Besides it is advisable for him to review carefully the accumulated animal data and he should anesthetize several large animals with the new agent using the same kind of anesthetic machine he intends to use on his first human subjects.

And so we have followed an idea from its incipiency to a chemical entity, through the whole gamut of animal experimentation in the hands of the pharmacologist and left it in the clinic, which in the last analysis must pass the final approbation or disapproval.

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Clinical Evaluation

by

WALTON VAN WINKLE, JR.*

PROOF of the pudding is in the eating thereof, and likewise the evaluation of a new therapeutic agent depends upon the results of careful clinical trials under properly controlled conditions. The pharmacological and other laboratory studies of a new drug provide the rational basis for the clinical use of the agent, but only through adequate studies in humans can the precise place of the agent in our therapeutic armamentarium be determined.

The Objectives of Clinical Trials

Broadly stated, the principal objectives of a clinical trial of a new drug are a determination of the efficacy and safety of the product and the establishment of the conditions—such as dosage, method of administration, adjunctive therapy and precautions—that will assure its maximum usefulness. These objectives must be kept clearly in mind by the clinician in the planning and conduct of the clinical trial.

In planning a clinical investigation of a new product, the question of efficacy must be considered in the light of the therapeutic value of products already available for the treatment of the condition under study. The objective is, therefore, not only to evaluate the absolute efficacy but also the relative efficacy as compared to other products and other methods of treatment. The investigation must also be designed to reveal all possible toxicity with a view to determining the true incidence and severity of any untoward reactions. The results should permit an appraisal of the "relative safety" of the product. By this we mean the amount of therapeutic benefit that may be obtained and the seriousness of the conditions for which it may be useful, as compared to the undesirable properties and toxicity it possesses.

Information Necessary for Clinical Trial

The first principle to be observed in conducting any clinical investigation is that nothing must be done that may harm the patient. It is necessary, therefore, for the clinician to have certain information concerning a new drug before he administers it to patients for clinical trial. For instance, he should know the exact composition of the product, together with its physical and chemical properties. If a method of assay for the principal ingredient or ingredients is available, the clinician should be familiar with it. Information on the pharmacology, including the actions, toxicity and fate of the product in the body, is essential for intelligent clinical trial. Other laboratory data should be made available if pertinent to the product or study.

From the information furnished by the laboratory investigators, the clinician can plan the details of his investigation. He will be able to forecast the probable effective dosage and can estimate the probable duration of treatment. He should be in a position to select those laboratory studies that should be performed as part of the clinical studies and that will furnish an objective estimate of the efficacy of the drug and information on the early or subclinical manifestations of toxicity.

If, on reviewing the data obtained from laboratory studies, the clinician feels that the information does not demonstrate a probability that the new drug has therapeutic merit or that it may have serious toxic actions which overshadow any possible clinical effectiveness, he should decline to perform clinical trials. Furthermore, data necessary to reach such a decision may be lacking and he should so inform the sponsor of the drug, pointing out what information will be necessary before he can undertake an adequate clinical investigation.

Conditions for Competent Clinical Trial

Clinical investigation is not something to be lightly undertaken. The foremost requirement for the adequate clinical trial of a new drug is a competent investigator interested in the problem. All other considerations should be subsidiary to this. Good clinical research cannot be performed by investigators who are so eager to receive funds

* Secretary, Therapeutic Trials Committee, Council on Pharmacy and Chemistry, American Medical Association, Chicago 10, Ill.

or to produce papers that they will accept problems in which they have little interest or in fields for which their training and experience has not made them competent. Even the presence of extraordinary facilities cannot compensate for lack of interest or competence on the part of the investigator.

The second condition that must be met for satisfactory clinical investigation is adequate clinical material. If a study involves the clinical trial of a new agent for a disease such as amebic dysentery, the investigator must have access to sufficient cases of the disease to perform an adequate study. Obviously, many diseases are more prevalent in some sections of the country than in others; hence, the geographical location of the investigator is a factor for consideration.

Another condition that should be met before establishing a clinical trial is the presence of adequate facilities. Suitable laboratories, and equipment such as X-ray, ballistocardiographs, electro-encephalographs and other apparatus may be necessary for a complete study of the clinical actions of the new product. There must be sufficient hospital beds for subjects on whom the trial is to be made, and they must be readily accessible to the laboratory or other facilities to be used in the investigation.

Adequate professional and technical assistance must be available for proper carrying out of the details of the research project. Clinical trials require more than routine observation of patients and more than the ordinary diagnostic and therapeutic laboratory examinations. Competent and trained personnel must be available and have sufficient time to perform the necessary studies incident to modern clinical investigation.

Finally, no clinical investigation can be assured of success unless adequately financed. Professional and clerical assistance, supplies, hospitalization of patients, extra nursing care, overhead on use of institutional facilities and other requirements necessitate the expenditure of funds. These funds are usually derived from foundations, governmental grants, pharmaceutical manufacturing laboratories, or from the institution itself. The last-named source, however, is becoming less able to bear the costs of clinical research, and the funds usually have to be secured from the other sources mentioned.

Planning the Investigation

One of the most important parts of any clinical investigation takes place before a single patient is treated. This is the planning of the project. First, the clinician must set down the questions that he hopes to answer at the end of the investigation. With these questions clearly in mind, he must consider which among several methods of approach to the problem will be the best in each particular instance. The clinician's problem is much more difficult than that of the laboratory worker. Both deal with biological material which is variable in nature, but the physiologist, biochemist and pharmacologist can apply much more rigid controls than can the clinician. Isolation and study of individual organs or physiological systems is possible in the laboratory but seldom feasible in the clinic. Mice, rats and rabbits are bred for homogeneity but humans are among the most heterogenous of all species. The procedures that may be used for clinical investigation are limited by the needs and condition of the subjects under study.

To avoid being misled by his observations, the clinician must give considerable attention to establishing controls. This will be discussed in more detail later. It will be sufficient for the present to point out that the proper use of controls involves, in most instances, the application of statistical procedures; and consultation with a competent medical biometrist should be a part of every clinical investigation and should begin at the very first stage of planning.

With a knowledge of the pharmacological actions of the drug under study, the clinician may select those laboratory studies that should be performed concurrently with the usual observations on each subject. He must keep in mind, however, that the human species may not react like the laboratory animal, and he must utilize some laboratory observations that might not seem indicated by the results of pharmacological evaluation. This is particularly true in the case of drugs that may sensitize or to which individuals may show an idiosyncrasy. Dinitrophenol and thiouracil are good examples of drugs to which a large portion of the population show idiosyncrasy, while the sulfonamides are examples of drugs causing appreciable sensitivity. Such reactions were not predictable on the basis of animal studies. The plans for a clinical investigation must include a provision for observations that will detect and measure idiosyncrasy and sensitivity in the patients.

The available clinical material and the type of condition under study will affect the plans. Patients who must be observed while ambulatory cannot be subjected to as close observation as those that are hospitalized. Extremely ill patients cannot be subjected to extensive or ex-

hausting diagnostic or therapeutic manipulations. The procedures chosen as aids in the clinical trial must be selected with these limitations in mind.

The number of cases to be studied cannot be determined with precision in advance. The natural history of the disease, the degree to which objective or quantitative measurements may be made and the reproducibility of the results are among the governing factors. Greater attention to this point will be given in the section devoted to evaluation of results.

Controls

All experiments, to be of value, must be controlled. The control of experiments involving biological material is difficult, and the problem of controls in clinical investigation is the most difficult. There are many types of control that may be utilized in clinical investigations depending on the nature of the problem and the amount of clinical material to be observed. If the clinical observations are to be of an objective or quantitative nature, the problem of control involves primarily the measurement of the natural variations in untreated patients of those processes that can be subjected to objective measurement.

This may be done in one of several ways. Each patient may be observed carefully for a period before treatment with the new agent is begun. This control period must be sufficiently long to establish with reliability the natural variations to be seen in the course of the disease. Thus, each subject serves as his own control. Obviously, in an acute or fulminating disease or one in which the natural tendency is to recover without treatment, a pre-treatment control period is not feasible.

The treatment of alternate cases with the new agent, allowing every other case to serve as a control, is another method which has been widely used. This method is valid only if both groups are sufficiently large to ensure that the control and treated groups are identical as to distribution of age, sex, severity of disease and other similar factors, and that the treatment of the control group is identical in all respects with that of the treated group except for the drug being studied.

Unfortunately, the evaluation of many therapeutic agents, particularly such classes of drugs as analgesics, hypnotics, local anesthetics and sedatives, must depend largely on the subjective responses of the patient. These responses are affected not only by the drug but also by many unmeasurable and unpredictable variables inherent within the subject and his environment. Furthermore, the observations on the part of the clinician may be biased by erroneous subjective impressions. It is imperative, therefore, in making clinical trials of such agents to establish controls that will diminish or prevent these variables from affecting the results.

One of the best methods is the so-called "blind-test, cross-over" technique. This involves the separation of the subjects into two or more identical groups and the administration of the drug to one group and the administration of a placebo under identical conditions to the other group. Neither the subject nor the observer should know who is receiving the placebo and who is receiving the drug. After a suitable period, the groups are reversed: the group receiving the placebo now receiving the drug and the group formerly getting the drug being administered the placebo. This "cross-over" of medication should occur halfway in the total period of observation. In this manner, each group serves as its own control as well as serving as a control for the other group. This procedure has the greatest chance of eliminating from the results the influence of subjective bias on the part of the observer or the subject.

There are many other schemes that can be used to control clinical observations, but these examples will serve to illustrate some of those more commonly in use. The object of all methods of control is to eliminate from the results the influence of variable factors not related to the actions of the drug. Furthermore, the proper design of an experiment will often permit a quantitative measurement of these variables and a qualitative separation and analysis of them and their influence upon the subject under study.

Methods of Clinical Research

The principal tool of clinical research is keen and critical observation. The keenness of observation is inherent in the successful investigator; the critical evaluation of the observations is developed by experience. The clinical investigator who is noted for his competence is one who sees what others have missed and who quickly separates the unimportant from the significant and places each separate observation in its proper relation to the problem as a whole.

Fifty, or even twenty years ago, clinical research depended almost solely on the observation of the patient under treatment. Today, the clinician has many mechanical and electrical aids to his natural senses. The proper selection and application of these tools calls for a profound appreciation of their usefulness and limitations. Clinical medicine is now not only an art but also

a true science. However, no mechanical or electrical device can ever replace the critical observation of the patient or the experienced evaluation of these observations by the trained clinician.

Before applying any method to a problem in clinical research, the method itself must be evaluated. Failure to do this has led to the misapplication of methods and erroneous conclusions derived from a failure to understand the limitations of the method or its inapplicability to the problem under study.

Today, we see reports of the clinical effectiveness of new drugs based solely on methods which have yet to be evaluated. For instance, rutin is said to decrease capillary fragility, but none of the proposed methods for the clinical measurement of capillary fragility can be regarded as established. It is not at all certain that any of the proposed methods actually measure the resistance of the capillaries.

The Wolfe-Hardy technique for the quantitative measurement of pain thresholds in human subjects has been widely used in the evaluation of analgesics. However, expert neurophysiologists question whether this method actually measures pain. One must accept with considerable reservation results obtained by methods that are not fully evaluated or whose validity has not been established.

Many of the methods and procedures used in clinical research are familiar to all because of their routine use in the ordinary diagnosis and treatment of patients. The kidney and liver function tests, the various procedures for the study of blood and urine chemistry, the electrocardiograph and the metabolism measurements are all useful tools in the hands of the clinical investigator. Newer procedures are being studied and may soon have wide application both as research tools and as diagnostic procedures. Among these may be mentioned the electro-encephalograph, the venous catheter and radioactive isotopes. These have yet to be fully evaluated, but they hold promise of assisting the clinician in learning more concerning the actions of drugs in the human being and their effects on disease processes.

Clinical Research

Because of the fact that the various procedures used in clinical research require special skills and training both in their application and interpretation, the clinician must become a member of a team. Under his guidance, various specialists and technicians, such as the pathologist, radiologist, biochemist and bacteriologist contribute their knowledge and skills to the solution of the problem. In this atomic age, many clinical problems require the assistance of the physical chemist and physicist. The methods and techniques of other sciences are being adapted to clinical research and problems are being solved by teams of specialists all working toward a common goal through a cooperative effort. Such teamwork is in itself a "method" of clinical research.

Evaluation of Results

No research is complete with the mere establishment of new facts. Until these facts have been placed into proper relation to other facts and existing theories examined in the light of these data, the research is only partially completed. The planning and carrying out of clinical research is difficult, but the evaluation of the results is even more difficult and fraught with many pitfalls for the unwary.

Proper planning and the intelligent use of controls will, in most instances, simplify the problem of evaluation of the results of clinical research. However, there are certain points that must be considered by the clinician in evaluating the data which he and his colleagues have gathered.

The first point for scrutiny is the question of the reliability of the data. All tests, measurements and observations of biological material are subject to four sets of variables which influence the results.

Environmental variables are perhaps the easiest to recognize and control. The effect of such things, as barometric pressure, environmental temperature, humidity, noise and season of the year on the actions of some drugs in some patients is well known. If not under the control of the investigator, these variables can be measured with fair precision.

Since the human species is heterogenous, there exist marked variations in individual responses to drugs, both quantitative and qualitative in nature. Furthermore, within a single individual, there are variations in response depending on such factors as metabolic state, emotional tension and the presence of disease. The observer himself may be affected by similar factors so that under high emotional tension, he interprets an observation in one direction while a similar observation made under other circumstances may elicit an opposite interpretation.

Finally, the methods themselves are subject to inherent errors which should be known and considered in evaluating the results. The clinical investigator must scrutinize his data with these considerations in mind and decide upon their reliability. In this task, he may call upon

his statistical associate who has at his command various tests which may be applied to the data and which will give a measure of their reliability.

The significance of the data must also be examined. The data may be highly reliable in that each observation represents the true state of affairs at the time of observation; but the question arises as to whether the differences between one set of observations and another set are real or could have been found by chance. In other words, are the observed differences between a control group and a treated group, for instance, significant? Here again, the statistical colleague can tell us what the probablity is that the difference is or is not significant.

From the opposite viewpoint, the differences between groups, and hence, the effect of the drug under study, may be shown to be highly significant from the statistical standpoint, but this difference when examined from a common sense standpoint, may not be of any practical importance. A drug may be shown to produce a 20% better analgesia than some other drug, and by statistical analysis this 20% difference can be shown to have a high probability of significance. It is extremely questionable, however, that this difference is of sufficient magnitude to be of practical importance, and from the standpoint of therapy the new agent should not be regarded as a superior analgesic just on this basis.

Finally, the statistician may be able to condense and group the data in such a manner that relationships not readily apparent before become clear. Such statistical manipulations must be made intelligently in order not to produce false relationships or obscure important findings. When properly done, such condensations and groupings assist others, not familiar with the problem, in their understanding of the results obtained and their significance.

Future Trends in Clinical Investigation

For centuries, clinical research has been largely an individual undertaking. However, with the advancements in our knowledge of human physiology and pharmacology, the complexities of clinical investigation have made it virtually impossible for the lone investigator to bring a major problem to a satisfactory conclusion.

The clinician now seeks the aid of his colleagues in the solution of his research problems. In many instances, however, the resources of a single institution are insufficient for the complete solution of clinical problems involving new drugs and cooperative projects between groups of investigators have been found to provide the best results in the shortest time.

This trend toward cooperative research has also been advanced by the expanding activities of manufacturing pharmacy in the research field. In the development of new drugs, pharmaceutical firms have frequently sponsored cooperative research among different institutions and have found that such efforts lead to quicker and more adequate solution of problems than concentrating all phases of the problem in one institution.

The recent war, however, produced for the first time in this country a nationwide program of cooperative medical research. The benefits of this program have been so apparent that a demand for its continuation in principle has been voiced in many quarters. The proposal for a National Science Foundation, the formation of the Committee on Growth and other similar

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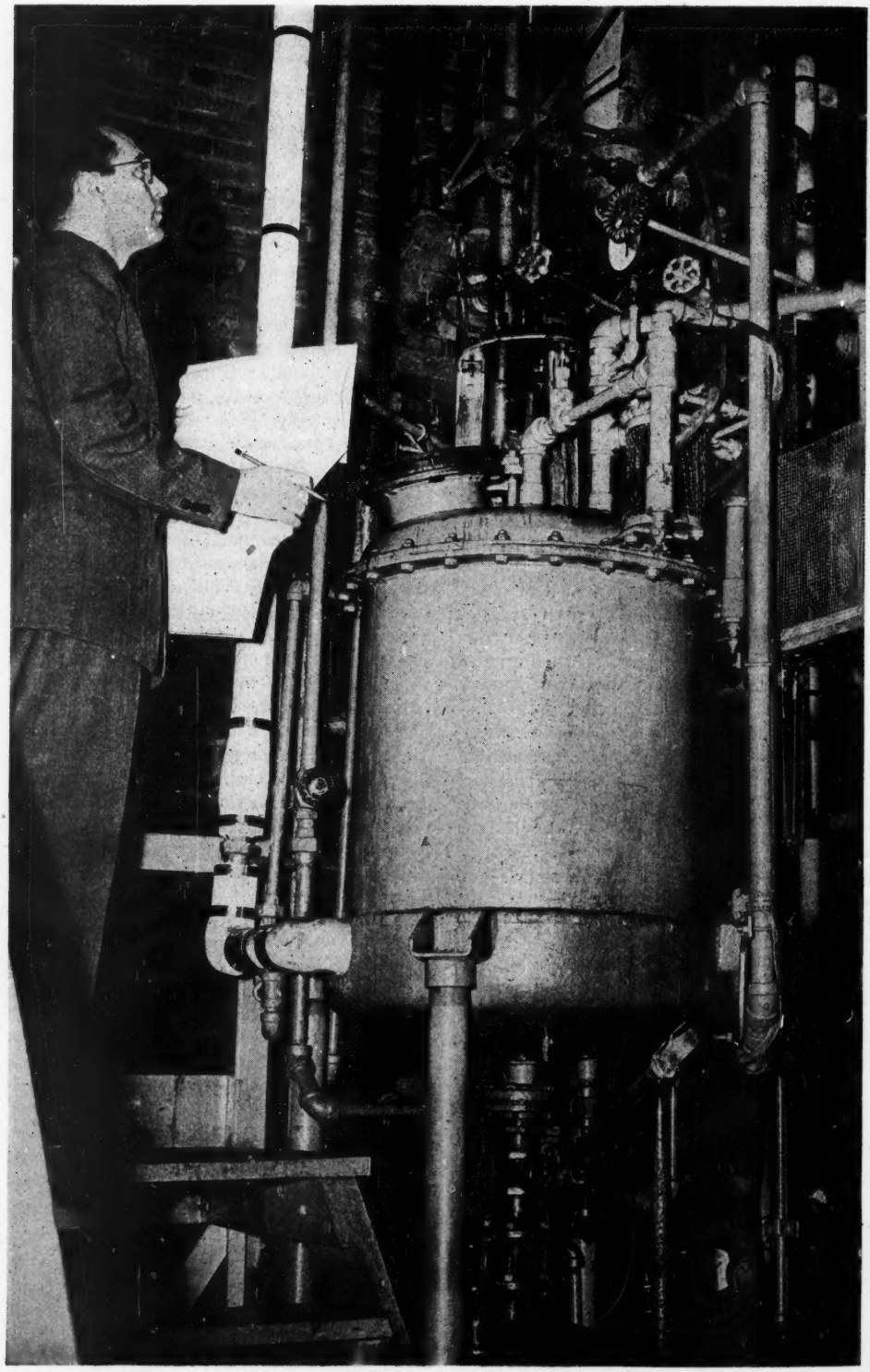
WALTON VAN WINKLE, Jr., author of "Clinical Evaluation," is secretary of the Therapeutic Trials Committee, Council on Pharmacy and Chemistry, American Medical Association. He was with the Food and Drug Administration from 1941 to 1946, advancing from associate pharmacologist to medical officer and assistant medical director in charge of the New Drug Section. Dr. Van Winkle holds degrees in both biochemistry and medicine. While studying for his medical degree at Stanford he was research assistant in pharmacology and later served as instructor for two years. He has also lectured in pharmacology and medicine at Georgetown University and the University of Illinois. Contributions to the literature have been in the fields of biochemistry, pharmacology, clinical research in industry, methods of laboratory and clinical appraisal of new drugs and determination of their safety.



The Chemical Engineer

by

P. G. COLIN* and H. E. SILCOX†

EXPANSION of pharmaceutical industry into large-scale production of a host of new fine chemicals and antibiotics has made it necessary to draw upon the talents of the chemical engineer, which supplement the knowledge and experience of the chemist and microbiologist, to assure the most practical and economical production. This development has come to the fore during the past ten years. The advent of processes for synthetic vitamins, sulfonamides, insecticides, and the antibiotics penicillin and streptomycin has made it necessary to abandon many time-honored methods of production. Not only labor economy motivates this change; in many cases improved methods of production result in higher yields and quality of product.

Chemical engineering is concerned with developing and applying manufacturing processes involving chemical or certain physical changes of material. These manufacturing processes usually resolve into a coordinated series of unit chemical processes and unit physical operations. The work of the chemical engineer primarily concerns the development, design, construction and operation of equipment and plants in which these unit processes and operations are applied. Chemistry, physics and mathematics are the underlying sciences of chemical engineering, and economics is its guide in practice.

The chemical engineer as an individual, however, must adapt himself to the particular field of chemical manufacture in which he is working. Chemical manufacturing may be subdivided logically into two fundamental fields, the heavy and fine chemicals. These two fields differ primarily in volume of production and complexity of process, introducing many secondary considerations which affect the responsibilities of the chemical engineer.

The development of a new pharmaceutical chemical from its conception to routine production is a cooperative project requiring the closest teamwork by the contributing groups. Development of a new product often begins with exploratory work in a "pioneering" research group followed by amplification and improvement in the hands of the "developmental" research chemist or microbiologist. At the appropriate time in the development, the development chemical engineer is assigned to the project.

His function is to study the process in cooperation with the developmental chemist and to establish the method by which the process is to be handled in production equipment. His responsibility is to establish the size and type of equipment and the operational details that will produce the product with yield and quality at least comparable to those obtained by the developmental chemist.

In parallel, other chemical engineers will produce limited amounts of the new material in the pilot plant production equipment to establish more fully the chemical process and make available to qualified experimenters or clinicians sufficient quantities to ascertain the place of the new product in medicine and pharmacy.

Again, at the appropriate time, design engineers are assigned to the project to transform recommendations of the developmental chemists and chemical engineers into a plant layout and process flow sheets. Responsibilities of the design engineer involve evaluation of plant location, buildings and services in addition to the chemical engineering design of the operational equipment. In so far as process operation is concerned, approval of the plans by the development groups is required, and when agreement between the cooperating groups is reached the process is "frozen." In complex process developments, experience has shown that certain phases of the process may be completed and "frozen" prior to other phases.

With the design engineer rests the responsibility of purchase and installation of equipment and, when installed, demonstration of mechanical fitness. Following this mechanical demonstration, the development department accepts the equipment and proceeds into process operation.

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It is the responsibility of the development men to demonstrate process operation in the units, train men for the ultimate process supervision and prepare the final operating instructions along with all control testing procedures.

Up to this point, the development division has been responsible for the maintenance of operation of the entire process. Now this responsibility is transferred to the production group and the product is considered to be "on the line."

It is realized that the above outlined development procedure is not that used by all pharmaceutical manufacturers. However, this procedure has been used extensively during the past few years, and experience has shown that it can be followed quite successfully. The success of this procedure involves the close cooperation of the microbiologist, chemists, and chemical engineers, resulting in the economic production of a high quality product in the shortest possible time.

Unit Processes and Unit Operations

As previously mentioned chemical manufacturing processes usually may be resolved into a coordinated series of unit chemical processes and unit physical operations.

A *unit chemical process* may be defined as the conditions and equipment by which a type chemical change is accomplished. Hydrogenation, halogenation, nitration and sulfonation are among those referred to as unit processes. The large-scale production of fine chemicals has been made possible by the development of specialized unit process equipment to carry out reactions that a few years ago would have been limited to the laboratory.

A *unit operation* may be defined as the conditions and equipment by which a type physical change involved in chemical production is accomplished. Heat transfer, fluid flow, filtration, extraction and drying are among those referred to as unit operations. These unit processes and unit operations are the building blocks by which both simple and complicated processes have evolved.

These unit processes and operations have had a rapid but logical development. The chemist carries out most of the fundamental chemical and physical changes required for the preparation of a compound in the laboratory with relatively simple glass equipment. In small scale production, one finds the counterpart of this laboratory equipment, which is similar in design. As the scale of production increases, these units are often inefficient with respect to labor, space and raw materials, and in order to meet economic requirements, engineering improvements are sought for the several steps involved.

In many cases, it is possible to draw on unit processes and operations which have previously been developed; in instances where this is not possible, new unit processes and operations are evolved from the laboratory methods. In this manner, an increasing number of unit processes and operations are made available as the "building blocks" for future products. Some of these are discussed below as specific examples of the chemical engineer's work.

Filtration of Antibiotic Broths

In the organic laboratory, the customary method of filtration is use of the Büchner funnel. This method has its counterpart in production as a unit known as the filter pot. Although the filter pot is still used for certain small scale applications, the advent of large scale filtration operations has brought about the introduction of more efficient methods of filtration. The filter press, the centrifuge and the continuous rotary filter are being used more frequently as the mechanisms for production filtrations.

Several years ago when antibiotic production was first being contemplated, the filter pot was used for broth filtration of the initial small production. As production increased, it became apparent that such a filtration mechanism would not only be impractical but also impossible. The next unit tried was the centrifuge, but because of broth characteristics this method soon gave way to the plate and frame filter press. As antibiotic production pyramided, it soon became apparent that several hundred thousand gallons per month of these comparatively unstable broths, containing mycelia and slimes, would have to be filtered at prescribed temperatures within short time limits. After considerable experimentation, the continuous rotary filter was chosen.

In production, rates of several thousand gallons per hour have been maintained using rotary pressure precoat units with advancing knives and spray washing. The continuous presentation of fresh filtering surface by the precoat filter has made it possible to attain high filtration rates and high antibiotic recovery, and the use of this filter has been one of the important contributions to large scale antibiotic production.

Countercurrent Extraction of Penicillin

The chemist generally carries out solvent extractions in the laboratory by the conventional cross-extraction batch method in a separatory

funnel. The large scale counterpart of the separatory funnel, the batch extractor, has been used in industry from the beginning of the production of organic chemicals. Today this method may not be adequate where large volumes of solvent must be handled and where the recovery of product and solvent is of paramount economic importance. Many of the large scale extractions now being effected for fine chemical isolations are based on continuous countercurrent column units that permit economy of solvent, equipment and labor.

Solvent extraction is used considerably as part of the penicillin isolation procedure. At the outset these processes were based on cross-extraction. As production increased, the solvent volumes became more important not only because of cost but also availability during the wartime shortages. Also, it was shown that penicillin was quite unstable under conditions of extraction, and it was essential to utilize rapid mixing and separation at controlled temperatures. To meet these conditions, special units were assembled that allow rapid mixing and centrifugal separation on a countercurrent basis. These effect efficient transfer of penicillin into and out of organic solvents.

When penicillin was first made available, the potency (and thus the purity) of the final product was low. This was due to the presence of impurities other than penicillin that exhibit properties similar to the active penicillins. By quantitative evaluation of the extraction properties of the impurities and the determination of the slight differences in distribution coefficients, it has been possible to extract penicillin selectively by the imposition of very closely controlled extraction conditions. Although it has not been possible to produce pure penicillin by extraction alone, these improvements in extraction techniques have contributed much toward making a high-purity product available.

Evaporation of Heat Sensitive Solutions

Many solutions of organic compounds exhibit a time-temperature instability with respect to the desired constituent, but in many processes it is necessary to concentrate large volumes of sensitive solutions by evaporation. Carrying out these concentrations in conventional batch stills results in subjecting the product to long periods of heating, thus enhancing deterioration. To hold contact with heat to a minimum, generous use is made of circulating and long tube evaporators. The latter, in particular, subjects the liquid to elevated temperatures only for a few seconds. In special cases, wherein even a few seconds at a high temperature is detrimental, these units can be operated under vacuum with the heat of evaporation being supplied by steam at subatmospheric pressure.

Where large volumes of liquor of greater stability must be concentrated, advantage may be taken of multiple effect evaporators to procure steam economy.

Chlorination of Alcohol for DDT Production

For many years chloral hydrate was produced on a small scale by the chlorination of alcohol. This chlorination was made in ceramic equipment by bubbling the chlorine through alcohol, the reaction requiring about twenty days for completion. During the war, large scale uses for the insecticide DDT developed very rapidly and, since DDT is made by the condensation of chloral and monochlorbenzene, it is readily apparent that large scale production was to a great extent dependent on the development of a more efficient process for the production of chloral.

Through a detailed study of the reaction kinetics of the chlorination and through proper choice of materials of construction and equipment design, it has been possible to reduce the time of chlorination to a small fraction of that originally required without making any change in the fundamental chemical reaction. This particular development has played an important part in making DDT available on a large scale.

Antibiotic Fermentation

The first penicillin made available for use was produced by surface fermentation in glass bottles. These bottles were capable of yielding approximately 0.5 L. of broth after several days of fermentation. Even in small scale operation, the number of bottles to be handled made the process unwieldy. It was necessary at that time to carry out this fermentation under conditions of shallow liquid depths since the fermentation was aerobic. The first step toward large scale production was to carry out the fermentation in stacks of shallow trays placed in a steel shell. Before these units were put in operation, however, microbiologists developed a mold strain capable of submerged production of penicillin, which was adaptable to tank fermentation, provided air was introduced through spargers into the fermenting batch. Based on this development, the steel shells for holding the shallow trays were converted to deep tank fermenters. Since that time these deep fermenters have been modified to incorporate agitation, improved

methods of air dispersion and many other features shown advantageous for antibiotic fermentation. In the short space of five years, the original bottle fermentation has evolved to the 15,000 gallon fermenters which are used for the fermentation of streptomycin.

Sublimative Drying of Pharmaceuticals

The many intermediates and final products handled in the industry require essentially every type of drying device. The conventional tray dryer has been augmented by vacuum shelf and rotary units, continuous dryers of the belt, flight, drum, flash and spray types. The flash and spray dryer units are particularly useful in handling temperature sensitive materials, since the drying time is limited to a few seconds.

The preparation of sterile products, such as blood plasma, penicillin and streptomycin, has introduced the technique of sublimative drying, an operation known as lyophilizing. The sterile water solutions are frozen at temperatures of the order of $-40°$ C. and then placed in cabinets provided with careful temperature control and high vacuum. Under these conditions, the solution remains frozen and the water is removed by sublimation. The vacuum is attained by the use of specially designed condensers and high vacuum pumps.

Solvent Recovery and Waste Disposal

The large scale production of fine chemicals gives rise to many problems in addition to the process for the production of the chemical itself. For reasons of economy, large volumes of process solvents must be recovered and, in keeping with public safety, harmful vapors and solutions must be rendered harmless. Distillation is the most widely used operation for effecting solvent recovery. Some mixtures of solvents may be separated readily; however, many mixtures give rise to maximum or minimum azeotropes or may be difficult to separate economically due to closeness of boiling points. During the past few years, the chemical engineer has drawn on new techniques for effecting separations, namely azeotropic and extractive fractionation. Both of these techniques involve the addition of a new component that alters the relative vapor pressures of the components to be separated.

Many waste liquors contain organic constituents that impart a high biological oxygen demand. This demand is sometimes so high that the liquors cannot be admitted to open streams. To effect disposition, these liquors are first evaporated to a syrup and then subjected to incineration. Many waste filter cakes are also disposed of by incineration.

Noxious waste gases must also be eliminated. In the preparation of chloral for DDT production, large quantities of HCl are evolved. In this particular case, the gas is absorbed in water to give hydrochloric acid, which has value in itself. Not only does the recovery of HCl produce a by-product extensively used in the chemical industry but, were this not possible, large quantities of neutralizing agent would be required, adding to the cost of the DDT. Thus, in this particular case, a by-product that was a potential liability was converted to a process asset.

Selective Adsorption

There are many examples where mixed components with similar physical properties have been separated successfully by fractionation processes. These processes depend on variations of (1) solubility in the case of fractional crystallization, (2) vapor pressure for fractional distillation, (3) distribution coefficients for fractional extraction and, more recently, (4) adsorption coefficients for fractional adsorption.

In the latter case, the ion exchange resins are rapidly taking an important position as one of the tools with which chemical separations may be effected. The use of activated carbon as an adsorption agent has also been extended and processes for the recovery of penicillin and streptomycin have been used in which carbon adsorption was one of the important steps.

With the development of practical methods for selective adsorption and desorption, it can be seen that one more method is available for the isolation of desired components from impure mixtures. Many products, such as the antibiotics, carry a variety of impurities in the initial form. Only after a careful quantitative study is made of both product and impurities can a process be evolved that will yield a product of the desired purity. Many times the ultimate process is based on a combination of these selective separation methods.

Chemical Equipment Selection

The fine chemical industry has reached maturity by the development of equipment for effecting essentially all the classical organic reactions and essentially every known mechanism of isolation and purification. During the past few years, the availability of standard chemical equipment has improved markedly but many times the engineer must design his own equipment. The selection

of the component equipment parts of the process is a major responsibility of the chemical engineer, complementing proper selection of chemical processes on the part of the chemist. This selection of equipment and the subsequent operation and control contribute markedly to the economic production of high quality products in the shortest possible time.

The industry is required to handle so many highly corrosive components and mixtures that, except for utilization for service lines and storage tanks, the use of conventional steel is the exception rather than the rule.

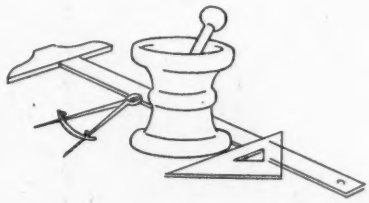
Today, stainless steel, corrosion resistant alloys (such as the Hastelloys and Durirons), glass, porcelain, Karbate and enamelware are the essential materials of construction. Plastic coatings and rubber linings are also used advantageously to protect against the corrosive nature of chemicals. However, the industry is still very much in need of improved metals that offer resistance to such materials as the halogens and halogen acids.

Responsibility of the Chemical Engineer

The foregoing discussion has emphasized the functions and responsibilities of the chemical engineer. Although the chemical engineer assumes an early role during process development and is intimately connected with the process throughout development and into the routine production stage, rarely does he alone bear the responsibility for development of the process in its entirety.

In all stages of process development and production, it is necessary that he work cooperatively with men from other departments. It is only under such conditions that the highly specialized and exacting procedures involved in pharmaceutical production can be extrapolated from the laboratory to successfully controlled operation in large scale equipment as actually used in the plant.

Through these cooperative efforts, large scale production of the vitamins, sulfonamides and antibiotics, along with a host of other important drugs, has become a reality, thus making them available for wide use in therapy. In addition to availability, continued process development and improvement of equipment have and will continue to effect economies that will be reflected in lower cost to the practicing pharmacist and to the patient.



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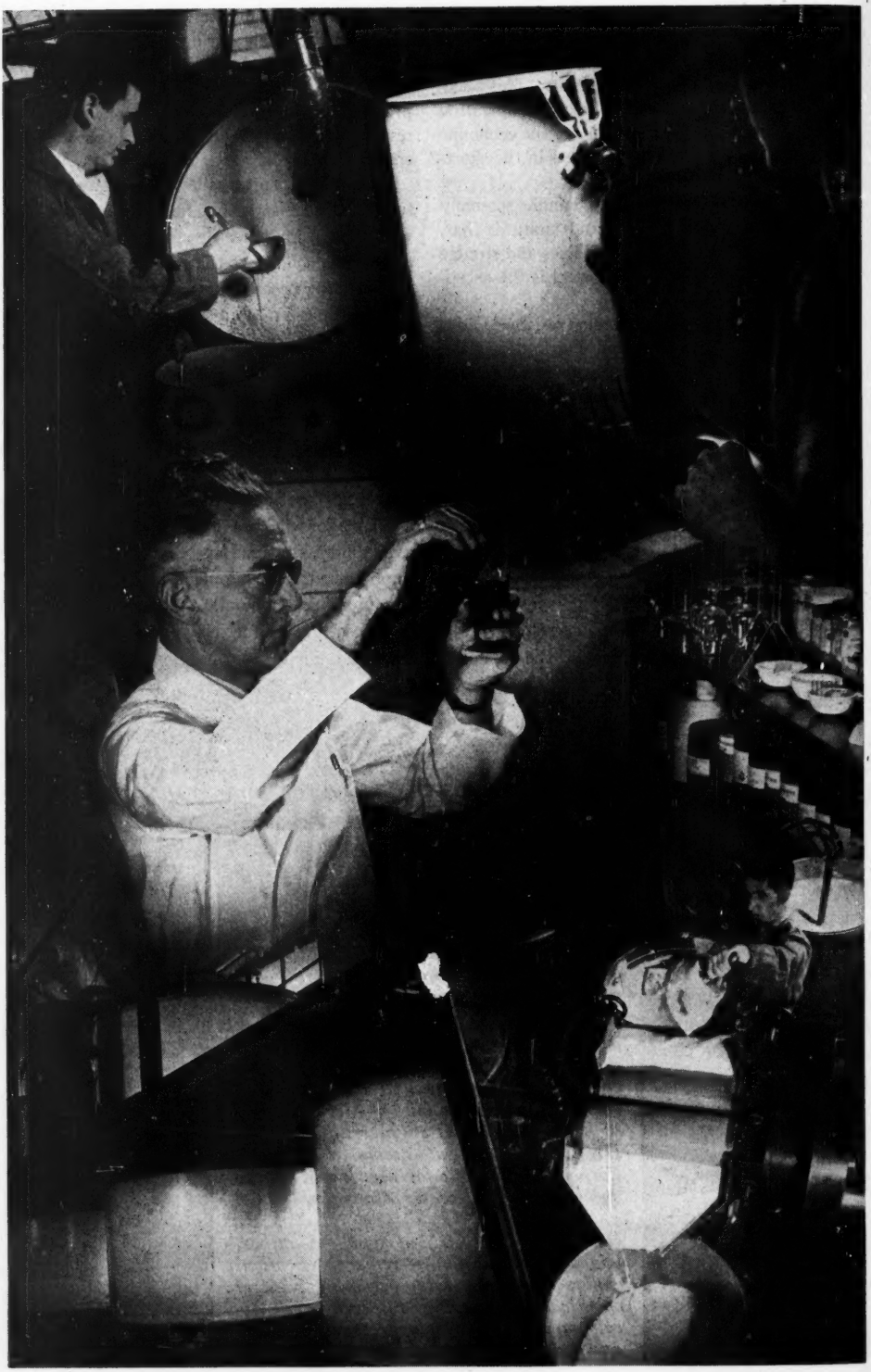
HERBERT SILCOX {right} co-author, joined Merck & Co. as research chemical engineer in 1942, later becoming head of chemical engineering research and development. He holds degrees in chemistry and a doctorate in chemical engineering.



Product Development

by

CHARLES F. LANWERMEYER*

THE pharmacist and pharmaceutical chemist usually exert their influence in the development of a new drug just before the final product is completed. However, the more knowledge the pharmacist gains of the early developmental work, the better he can perform his definitive functions.

The organic chemist, biochemist and bacteriologist constantly are creating new compounds, which may or may not have medicinal value. The therapeutic virtue of a new drug is studied first by the pharmacologist, who tests the preparation on animals. If it is shown to have medicinal value, the drug is then studied by the clinician, who administers it to patients. These two investigators determine the approximate dosage necessary to produce the expected results. They indicate the route by which the drug should be administered, whether it should be injected or taken orally, whether it may be sprayed into the nasal or oral cavities, inserted into the rectum or vagina, or applied externally.

The pharmacist's skill and ingenuity then come into play. For the new drug must be made available in its most practical form, for use by the patient. For a drug to be of greatest value, it must be in a form that the practicing pharmacist can dispense to the patient from the prescription counter. Too, the pharmacist must be able to formulate practical preparations to be used either by the physician, the dentist or the veterinarian. Years ago, the individual practicing pharmacist prepared his own elixirs, emulsions, ointments, suppositories and capsules at the prescription counter. Advances in modern medical science have made this method of drug preparation practically an impossibility in many instances. The task has now been taken over by certain highly specialized pharmacists, who have chosen to use their scientific training for the industrial development of new drugs and pharmaceuticals.

In formulating a new drug, the research pharmacist attempts to build into the product enduring qualities of pharmaceutical elegance and stability. Not only must these qualities last for a few days, as do the prescription counter preparations, but they must endure for the length of time the product remains on the pharmacist's shelf.

These qualities of elegance and stability allow the practicing pharmacist to dispense the products with full confidence in their effectiveness. Also, they prevent any question of doubt in the patient's mind concerning the quality of the medication when a prescription is refilled; for the drug looks, smells and tastes the same the second time as it did the first time he received it.

Injectable Preparations

Drugs for injection are manufactured either as ampuls, cartridges, vials or in bulk solutions. They are intended for injection by the intravenous, subcutaneous, intramuscular or intraspinal route. The drug must be in some solvent that is compatible with it and that will not react with the drug to form a different compound.

The solvents used in the manufacture of injectable solutions may be chemically pure water, physiological salt solution, Ringer's Solution and isotonic dextrose solution. Sometimes buffers, acidifying agents or alkalinizing agents may be added.

If the drug is insoluble in aqueous solutions, it must be dissolved in some vegetable oil such as almond, olive, peanut or sesame oil. Less viscous oil media may be necessary, such as the vegetable oil esters; or more viscous media may be required, such as vegetable oils to which certain waxes have been added.

Some drugs, which are insoluble in aqueous media, are intended to exert their action over a prolonged period of time. Hence, they have to be suspended in an aqueous medium containing vegetable gums to increase the viscosity.

Certain other drugs are chemically unstable in either aqueous or oily solution. These drugs must be dispensed in powdered form, to be dissolved just before the physician uses them. Injectable products also may be dispensed as crystals, to be dissolved in certain body fluids, such

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as spinal fluid. These solutions are made just prior to use.

In addition to the solvents used, certain chemicals such as the bisulfites, buffer salts, alkalis and other nontoxic solubilizing agents will often be indicated as stabilizers. In multiple-dose vials, bacteriostatic agents must be used, such as phenol, chlorobutanol and benzyl alcohol. In this way the product remains sterile regardless of how many doses are removed from the vial.

Containers also play an important role in pharmaceutical elegance and stability.

The size of an ampul may vary from 0.5 cc. to 100 cc. The size of a cartridge is usually 0.5 cc. to 2 cc. Vials used as multiple-dose containers usually vary in size from 2 cc. to 100 cc. Bulk solutions require single-dose containers and are given intravenously; the size varies from 250 cc. to 2000 cc.

If an ampul is indicated as the container for the new product, the specifications as to type of glass, the method of cleaning and sterilizing ampuls, and other requirements are stated completely in a 10-page monograph on ampuls in the National Formulary. Any question that arises can usually be settled satisfactorily by referring to this monograph.

If a cartridge is indicated, the composition of the stopper and plunger, and even the lubricant which is used on the plunger, may affect the contents. The stopper must fit tight enough to permit perfect sealing of the cartridge; its composition must permit penetration by a hypodermic needle without cutting out a core that may plug the needle or contaminate the contents. The plunger must fit tight enough to form a perfect seal, but must have enough slip so that when used as a plunger all the contents of the cartridge can be expressed.

If a vial or multiple-dose container is indicated, the glass must be of a quality that does not react with the contents. The stopper, usually of a rubber composition, must form a tight seal to protect the contents, be flexible enough to allow repeated puncturing with a hypodermic needle without coring, and be resilient enough to close the needle puncture after withdrawal of the required dosage. Further, the stopper must be of a composition that does not react with the contents.

If the drug is affected by exposure to light, an amber colored or other colored glass may be required, or the product may require a package that prevents undue exposure to light.

If a bulk (liter) solution is indicated the glass must be nonreactive with the contents. The closure must be of such composition as to make a tight seal. While this seal must not be affected by bumping during shipment or handling, it must be easy to remove and practical for use at the bedside.

As an example of how the finished product is dispensed, we might cite one of the vitamin B complex factors: Thiamine hydrochloride may be intended for use in ampuls of 1 cc., containing 50 to 100 mg. of thiamine hydrochloride per cc. It may be contained in a vial of 100 cc. of solution, each cubic centimeter of which contains 50 to 100 mg. of thiamine hydrochloride, in order that the physician may vary the dosage. It may be intended for intravenous use (bulk solution) containing 100 mg. per liter. Since thiamine hydrochloride is most stable at a *p*H 3.5, the contents as well as the container must be of such composition that that *p*H is not affected.

How is stability ascertained? The finished product is exposed to a temperature of usually 105° F. for a prolonged period of time. Assays for potency of the active ingredient, *p*H determinations, observation of the color, clarity, sterility etc., are made at regular intervals. If all characteristics are satisfactory, then the pharmacist may be assured that the product has the properties of pharmaceutical elegance and stability, which justify its distribution through the hospital or prescription pharmacy.

Oral Preparations in Liquid Form

These preparations may be elixirs, emulsions, fluidextracts, tinctures, syrups or solutions. To prepare the drug properly the pharmacist must know its chemical and physical properties. He must also know its compatibilities with other drugs and vehicles. If the drug is of botanical origin, the proper menstruum for extracting the active principles must be ascertained. If it is a chemical, its solubilities in various solvents must be determined.

After the active ingredients—either drug extract or chemical—are in solution, preservatives, such as alcohol, glycerin or sugar, must be added to prevent mold growth or fermentation in the finished product. Then, since elegance is one of the pharmacist's ideals, flavors, sweetening agents, coloring agents and other ingredients must be added. The drug then becomes pleasing to the senses of taste, smell and sight. If the product is a tincture or fluidextract that is usually mixed with vehicles, the factor of palatability is not so important; but if it is an elixir, syrup or solution, the factor of palatability is of greatest importance. If it is an emulsion, palatability and physical

stability are important. If an emulsion separates so that it cannot easily be re-emulsified simply by shaking, then the pharmacist has neglected an important requirement in a finished product.

Containers

A container must be chosen that will preserve the original properties of the product. Care must be taken that the bottle or even the liners used in the cap closures do not react to cause the product to become unsightly or even physiologically inactive. The stability of the product is usually determined by exposing the preparation, in the final container, at either elevated or reduced temperatures for prolonged periods of time. Check assays of the ingredients, as well as checks of the color, odor, taste and clarity, are made at regular intervals to establish the "shelf-life" of the product. In some liquid preparations which are susceptible to decomposition by contact with air, saturation of the preparation with an inert gas, such as carbon dioxide or nitrogen, may be necessary. Or, the gas may overlay the preparation in the finished container.

Although a few of the difficulties that beset the pharmacist in developing a new product are covered in the pharmaceutical and chemical text or reference books, in general these books have not been able to keep up with the many ramifications. Due to rapid progress it has been necessary for the U. S. P. and N. F. to issue interim revisions of their standards for drugs, between the regular revisions of the books.

Oral Preparations in Solid Form

In the preparation of solid forms of medication, such as capsules, tablets and effervescent salts, as in the preparation of other types of medicaments, the pharmacist must know the chemical and physical properties of new drugs, as well as their compatibilities with other drugs.

Capsules are in two forms: dry-filled, and soluble elastic. Dry-filled capsules usually contain the drug in powder form, thoroughly mixed with an excipient or filler, such as starches, sugars or inert chemicals. The ingredients must be mixed and the capsules filled with exactness. If the contents of the capsule are hygroscopic, some adsorbent or desiccating agent may be required to prevent the contents from coalescing. The requirements of the drug might even necessitate the filling of the capsules in an atmosphere having a very low humidity, as in humidity-controlled rooms. If the drug has an obnoxious odor, the finished capsules may be coated with sugar or an enteric coating.

The shells of soluble elastic capsules are composed of a mixture of gelatin, and a humectant such as glycerin. They contain some moisture, and are usually used for drugs containing oils and fats with added dry ingredients. These capsules are made on an ingenious apparatus, where the slightest variation in consistency or in particle size of the mass may cause an unequal fill to the capsule, or even prevent the sealing of the two halves of the capsule body. Therefore, the pharmacist must select for his mass dry ingredients of the proper fineness; the final mass, furthermore, must have the correct viscosity. Stability is again determined by the shelf-life of the capsules at elevated temperatures.

Tablets are probably the most popular form of solid, dry medication for oral use. In manufacturing tablets, the active ingredients are moistened with some vegetable or chemical gum mixture. The mass is dried and is either sieved or mechanically broken to the proper granule size. A disintegrating agent such as starch is then incorporated plus some lubricant such as talc or mineral oil. The material is compressed to the exact weight on a compressing machine.

Some drugs do not permit moistening, massing and drying of the granulated material, without some decomposition. These tablets must be made by thoroughly mixing the new drug with inert binders, disintegrating agents and lubricants, and then compressing them into large tablets on compressing machines. This process is called "slugging." The "slugs" are then broken up, sieved to the proper granule size and compressed to the exact weight on a tablet compressing machine.

Regardless of which method is used, the finished tablet must be of the proper size, shape and weight to assure exact dosage in each tablet in the lot. If the new drug is affected by light, it may become necessary to compress the tablets in the dark. If it absorbs moisture, the tablets will have to be manufactured in a practically humidity-free room. Tablets must not change in color with age. The practicing pharmacist has difficulty in explaining to a patron that the yellow or brown tablets that he received on a refill prescription contain the same ingredients as those supplied on the original prescription in which the tablets were white.

Tablets must be hard enough to withstand packing, shipping and handling without chipping or crumbling. However, they must be soft enough to disintegrate rapidly. If colors or dyes are added to the tablets, they must be so standardized that each successive lot is the same shade as the previous one. Some tablets may re-

quire sweetening or flavoring to increase palatability. Most impalatable tablets, however, can be coated to cover distasteful properties.

There are two types of coated tablets: those which dissolve in the stomach, and those which dissolve in the upper intestine.

For the first group, the tablets to be coated are dusted with an inert powder. Then they are coated with a syrupy liquid. This is followed by another syrupy liquid that is colored. After each treatment the tablets are dried in coating pans. Then they are polished, usually with an inert, waxy solution.

Tablets that dissolve in the intestine are coated with an enteric coating, such as salol, keratin, resins or other substances. The appearance of these tablets is improved by a coating of syrup. Enteric coating is probably one of the most intricate processes with which the pharmacist is confronted. The enteric coating must be insoluble in the dilute acids of the stomach, but must dissolve promptly in dilute alkalis present in the intestine. Therefore the tablets often must be tested mechanically or chemically *in vitro*, or by fluoroscopic examination *in vivo*.

Stability of coated tablets is tested at elevated temperatures for a prolonged period of time. With enteric coated tablets, however, solubility determinations of the coatings and disintegrating time of the tablets must be added to the usual factors that the pharmacist must consider before he can produce an elegant, stable and efficacious product.

Troches and lozenges may also be considered as tablets. Many of these are made today by compression, similar to that used in tablet manufacturing. Whereas tablets are usually required to have a rapid disintegrating time, troches or lozenges must have prolonged disintegrating time. These products, therefore, must have some base or excipient that slows up the disintegrating time; also, they must usually be compressed very much harder than tablets.

Hypodermic Tablets

Although hypodermic tablets might well have been considered along with injectable preparations, they are treated here because of their method of manufacture, and because they are dry preparations. Hypodermic tablets must contain the new drug in its highest state of purity; it must be mixed with a base, usually lactose C. P. The ingredients are finely powdered and mixed thoroughly. Then, after moistening with a solvent, they are molded on triturate molds. This solvent is usually alcohol in various percentages, the percentage depending on the drug being pressed or molded. Instead of being molded, the hypodermic tablet may be compressed on a special hypodermic tablet machine.

Hypodermic tablets must dissolve clearly, completely and rapidly in one or two cc. of sterile water. They must be hard enough to withstand handling but soft enough to dissolve rapidly. Since they are used for injections, sterile precautions must be observed at every step of manufacture.

Effervescent Salts

Effervescent salts constitute a specialized group of preparations in which the new drug is mixed with acids and carbonates or bicarbonates, granulated and dried. The characteristics of the drug, in this form, again test the ingenuity of the pharmacist. The finished preparation, when it is dissolved in water, must make a clear, sparkling effervescent potion with all the properties of pharmaceutical elegance and stability. Sometimes colors or flavors may be added to effervescent products to increase their palatability. In the development of this type of product, the pharmacist must give attention to the type of container in which the salts are dispensed.

External Preparations

External preparations may be either in liquid, semisolid or solid form. Although liquids that are sprayed or dropped into the nose or throat may be classed as internal preparations, for the purposes of this paper they may be classified as external preparations. The new drug, if intended for use as a spray or inhalant, must be compatible with the diluent. The diluent may be a vegetable or mineral oil. It may be an aqueous suspension or an emulsion. The viscosity of the finished product must be determined and adjusted for the purpose for which it is intended. The colors and flavors used must be compatible with the new drug and the diluent, as well as being nonirritating to the mucosa on which it is to be used. Adjustments of the *p*H of the finished product are often necessary to assure stability.

Finally, the container in which it is dispensed must not react with and decompose the active ingredient. Mineral oil, particularly, has a tendency to creep, causing leakage of the container. The proper caps, cap liners and other closures must be studied so that the elegance and stability of the final product is assured. If a medicine dropper is used in the bottle, the composition of the rubber nipple must be ascertained and

so adjusted that it does not react with the contents of the bottle.

Lotions and Liniments

Lotions and liniments, if intended as a base for a new drug, have been covered adequately under the discussion of solutions and emulsions.

Ointments and Creams

Ointments and creams require treatment different from that mentioned previously. In ointments, the new drug is incorporated into a fatty base of petrolatum, lanolin or some of the newer waxes or wax-like compounds. The new drug must be compatible with the base, and the base must be of a consistency that allows it to spread evenly on the body area for which it is intended. The base for a denuded area of the body is different from one used on unbroken skin. The base of an ointment which is to be used for its analgesic and stimulating property, and which exerts its action by absorption through the skin, is different from one intended for an area of the body which may have been denuded by burning or irritation.

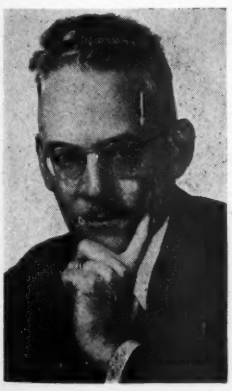
If the new drug is water soluble, or if it is intended to be rapidly absorbed, water often is is added to the ointment base. Such a base will be made of different kinds of fats and waxes, and the finished product will be either an emulsion or a soap. This mixture usually is called a cream. If the new drug is formulated as a cream, the rapid absorption of a particular drug in this form may cause irritation. Then the drug would be more satisfactorily formulated as an ointment.

The purpose for which the new drug is intended is the criterion that determines whether an ointment or a cream should be the final product. Fineness of subdivision of the active ingredient is important. Likewise, stability must be assured, because ointments and creams must remain physically stable at elevated temperatures.

Ointments intended for ophthalmic use require special treatment. The new drug should be in an ultra-fine state of sudivision or in solution. It must be of such consistency that it spreads evenly and rapidly over the eyeball. The base should not contain anything that may cause irritation. Ophthalmic ointments must be filled into pure tin tubes that are immaculately clean; even the liners used in the caps used on the tubes must be tested to assure that they do not react with the ointment. Since the base of ophthalmic ointments is softer than that of regular ointments, care must be taken that the product does not separate mechanically, by melting, in the tube. If that happened, the patient might get more action from the first application from the tube, than from later applications.

Suppositories

A new drug may be indicated for rectal or vaginal use, as suppositories. For rectal suppositories, the drug is usually incorporated in a base of cocoa butter, with or without the addition of a small percentage of wax to raise slightly the melting point. Or, it may be incorporated in a base that does not melt at body temperatures, but allows the drug to dissolve gradually out of the suppository base. Finally, the base may dissolve in the rectum, carrying the drug with it. Compatibility of the drug with a cocoa butter base usually does not present a serious problem in suppositories, as it does in other forms of medication. (*Continued on page 180*)



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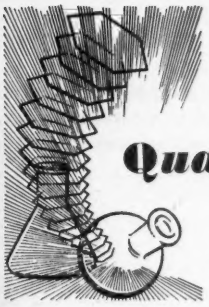

Quality Control

by

FRANK O. TAYLOR*

WHAT do we mean by "control procedures"? They are the means for obtaining facts on which to base sound judgment regarding the character, quality and uniformity of a medicinal preparation and regarding the statements that may be made concerning it in labeling or advertising. They are the scales on which to weigh the evidence of strength, quality and purity of each lot of the product.

Let us assume that the research laboratory has developed a substance having certain desirable medicinal properties. It may be a single definite chemical substance or a compound. This has been accomplished by the coordinated efforts of the organic chemist, the biochemist, the pharmaceutical chemist and the bacteriologist or microbiologist. With the aid of the chemical engineer practical manufacturing methods have been devised. The pharmacologist and toxicologist have determined its physiological action on animals in the laboratory, and it has received the approval of the clinician after suitable and comprehensive clinical trial.

It now becomes necessary to devise and apply methods of control so that each successive lot, and every package of each lot, can be certified to be of a specified composition and can be expected to have the same physiologic action and give similar therapeutic results.

While establishment of proper control procedure is the last step in developing any medicinal preparation, the working out of these controls is also usually a step by step progression beginning in the early stages of research upon the proposed new drug and continuing in close coordination with it from that point on. Moderate delay in the development of adequate control procedure in the early stages of research work may result in excessive delay in manufacturing operations.

These "control procedures" will include all appropriate tests and assays on the ingredients and finished product. If the final product is the result of a series of chemical reactions, similar tests and assays may be necessary on each intermediate substance that becomes in turn an ingredient for the next successive step of the whole process. There will also be required a complete record of all manufacturing and packaging operations, weighings, measurings, inspections, tests and assays with identifying signatures of each person responsible for any of these procedures.

This is a brief summary of general requirements. But it will be seen from more detailed discussion farther on in this paper that the scope of such control is extremely broad, extending into every factor that may affect the character and quality of the finished medicinal preparation. Furthermore it must be remembered that while this issue of the JOURNAL relates specifically to the development of new drugs, the basic principles of control apply equally to production of both "new" and "old" drugs. It does not matter whether a tablet of aspirin or of penicillin is to be made, the same principles of control, of weighing ingredients and checking these weights apply to both. Likewise if a proposed new drug is expected to cause a rise in blood pressure the method of control test may be identical with that used for years in the assay of epinephrine. On the other hand, again taking penicillin as an example, the general principles of a suitable method of assay were well known but a great amount of work was necessary to develop a specific assay for it and its preparations.

Importance of Proper Control

Nothing of so great importance to human welfare is used more completely on faith than a medicinal product. The physician diagnoses the illness of his patient and writes a prescription for what he considers to be a suitable medicament. The patient has confidence, or faith, in the doctor and in the probable help to be obtained from the prescribed medicine though he knows nothing about its character and medicinal action. The patient takes the prescription to the pharmacist who fills it. Both patient and physician must have faith that the pharmacist will adequately discharge his responsibility and dispense the desired medication in proper form. The pharmacist will know exactly the steps he takes to

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assure adequate performance of his duty, but in the prescription he will use one or more ingredients made by some manufacturer. He will know from his general scientific knowledge their character and therapeutic values but all he will know of the particular materials used will be the statement on the labels as to identity and quality. He in turn must rely upon his faith in the manufacturer whose product he uses. He cannot know from personal observation exactly what has been done in the manufacture and packaging of the particular lot of the drug from which he has used material to fill the prescription.

The manufacturer of the prescription ingredients is the only one who can know the details of production and packaging, and he of necessity becomes the anchor of this chain of faith and confidence. His is the final responsibility, and he must know fully all facts regarding the making, testing and packaging of the product of his laboratory.

It is essential that control procedures in his laboratory be adequate to establish and record all these facts. Here are the basic questions to which such control procedures must give the answers:

What is the character and quality of ingredients used?

Have they been properly used according to a previously worked out formula?

Is the finished product properly made?

Is it properly packaged and preserved?

Is it correctly labeled?

Responsibility for Control

The person responsible for the control of medicinal products, whether he exercises this function as a single individual in a very small establishment or as the directing head of an extensive division in a large laboratory, must be completely free from any domination by those responsible for production, or at least there must be a clear definition of the control and manufacturing operations.

The director of control must act essentially in a judicial capacity and render decisions that are fair and just, keeping always in mind the interests of the ultimate consumer of the drugs and maintaining the high standards of quality necessary to the thoroughly reputable producer of drugs. To this end there must be an understanding, by those responsible for manufacture and those responsible for control, of the varied problems which each group encounters. This is especially true in the case of new drugs where unexpected difficulties of manufacture may be encountered, and changes in control procedures may facilitate both production and control inspection.

Take for example the case of ampuls to be filled with a powder mixture, one ingredient of which is necessarily a finer powder than the other. This may at times result in a variation in electrostatic charge on the particles and a tendency toward slight separation. On-the-spot checks by some simple test or assay may disclose this promptly and prevent continued improper filling with subsequent rejection after final assay of a much larger quantity than would otherwise be the case.

Scope of Procedures

Control procedures must encompass all things that may influence the quality of the completed medicinal preparation; they must permit inquiry into every phase of purchasing, manufacturing, packaging, storage and labeling pertinent to the maintenance of uniform character and to the justification of label or advertising statements. Control procedures will range from the examination of samples of belladonna before purchase to the determination and identification of $^1/_{180}$ gr. of atropine in hypodermic tablets; from the examination of a ton of sarsaparilla for acid-insoluble ash (sand and dirt) to the micro-analysis of a milligram of sterol obtained from it; from the checking of the amount of alcohol in a tank-carload to the estimation by analysis of the amount of oxygen left in a 5-cc. ampul after it has been filled under partial vacuum.

These procedures will involve the use of a great variety of chemical and physical apparatus, such as: ordinary glass graduates for measuring liquids, or pipettes measuring in 0.01 cc.; platform scales to weigh in thousands of pounds or micro-balances weighing easily 0.01 mg. ($^1/_{6500}$ gr.); potentiometers or *p*H meters that will readily determine the difference in acidity between ten gallons of distilled water to which has been added *one drop* of hydrochloric acid U. S. P. and another ten gallons containing *two drops* of the same acid; microscopes, polariscopes, spectrographs, photometers, thermometers, pressure gauges and an almost unlimited variety of other apparatus.

Methods of control must also be applied to the character of glass in ampuls and bottles; to the quality of tin or aluminum in collapsible tubes; to the composition of closures for bottles and liners in caps; to the sterilization of solutions for parenteral use or of cotton for surgical operations;

to the detection of traces of pyrogenic substances in parenteral solutions; and even to the adhesiveness and water-resistant properties of glue for labels.

Applications of Control

We come now to the actual application of a system of control over the production of medicinal substances—or we might say, the mechanism of control. This will vary greatly in detail depending on the scale of operations controlled and the organizational arrangement of the particular laboratory in which it is applied. Nevertheless, the principles outlined in preceding paragraphs are the foundation for many variations in architectural form of the control structure. In this connection there should always be kept in mind, particularly with regard to "new drugs," certain requirements (relating to "new drug" applications) of Section 505(b) of the Food, Drug and Cosmetic Act, namely:

> (2) a full list of the articles used as components of such drug;
> (3) a full statement of the composition of such drug;
> (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
> (6) specimens of the labeling proposed to be used for such drug.

The discussion which follows is based largely on the writer's experience in administering an extensive and complex system of control. The comments or suggestions are in generalized form with some specific examples by way of illustration. Other ways of accomplishing the same ultimate purpose might be used by someone else, just as we might arrive at a geographical destination by two different roads, but the described procedures are known to lead to the objective sought. The order of discussion is that of the sequence of events in manufacture.

Ingredients or Components

The control of ingredients frequently begins even before they are purchased, with the examination of samples prior to purchase. This is more frequently the case with botanical drugs, especially those containing active principles measurable by methods of assay, so that the assay serves as a measure of both medicinal and monetary value. But not infrequently similar advance tests will be necessary where special specifications are required, such as the germicidal properties of a coal-tar distillate to be used as a base for a disinfectant or the vitamin content of a fish liver oil. Where ingredients to be used are described in the monographs of the U. S. P. or N. F. these standards may be referred to and purchase made on the basis of their specifications. But there will be far more primary ingredients than those so standardized, and it devolves upon the control department to set up specifications in such cases.

Applicable methods of assay or test may often be found in the publications of the Association of Official Agricultural Chemists, usually referred to in brief as the A. O. A. C., or in standards set up by the American Society for Testing Materials, more frequently referred to as the A. S. T. M. Both these organizations publish extensive volumes and shorter reports, although relatively few of the standards so published are directly applicable to materials for medicinal manufacture.

When samples are submitted for test prior to purchase at least a portion of these are retained for comparison until after acceptance of the entire lot purchased.

After a shipment of any material is received, the first step is to assign a serial number, usually called the "receiving number," which serves to identify it thereafter in all records of purchase, receipt, test and use. This number must appear on every package in addition to the customary label used by the shipper, and upon all records pertaining to the lot of material.

Sampling

The next step is sampling the entire lot for test before final approval and acceptance. The manner of sampling will depend upon the character of the material, the total quantity involved and the number and size of the packages. Suitable methods of sampling for vegetable and animal drugs are given in the U. S. P. and N. F. Analogous methods may be used in sampling chemicals, the exact procedure to be determined by the nature of the substance and its packaging. It is obvious that a single sample will accurately represent a tank-car of alcohol, but numerous samples would be required if the same quantity was supplied in 50-gallon drums. Likewise a single sample would be taken from a one-pound bottle of morphine sulfate, but this would not be satisfactory if the material was in 16 one-ounce packages. In such a case, however, a single sample for test might be prepared by thoroughly mixing small amounts taken from several of the bottles.

Care in taking samples may appreciably influ-

ence the conclusions derived from tests. For example, if a cold pint bottle is taken into a warm room a trace of moisture may condense on its inner surface. If the bottle is then quickly filled with heavy liquid petrolatum, this subsequently may fail to pass the "cloud test" due to the freezing out of the minute trace of water, although the oil itself is not defective.

Another point to be noted in accurate sampling is whether or not the supplier's control number is the same on all packages received. If not, then sampling on receipt should represent proportionally each control number, and it is well to assign subdivisions to the receiving number for accurate identification of each part of the lot. This can be done by the use of added letters as, for example, Rec. No. 245 and 245-a, or some similar device.

All tests must be permanently recorded and it should be an inflexible rule that no ingredient is to be used until it has been approved by the control laboratory.

The Product Formula

As previously indicated, the control department needs to take an early interest in the development of any formula so that proper control measures may be coordinated with all development in the research and product development laboratories. It is during this period that methods of test and assay may be adopted or modified as conditions demand. Each preliminary or experimental lot of any new product must be handled, so far as records are concerned, in exactly the same manner as the final and regular production so a survey of the system will apply to both. Here again it is to be noted that other systematic procedures for accomplishing the same end may be equally satisfactory, depending on size and type of operations, and organization of personnel.

The basis of all manufacturing operations is the master formula for each product. This master formula is kept in the exclusive possession of the control department, and from it all manufacturing formula cards are prepared, usually by photographic or photostatic reproduction. It shows the complete formula for a definite amount of the particular medicament, including names and quantities of *all* ingredients whether active or simply present as solvents, diluents, excipients, preservatives, flavors, colors, etc. If the formula is for some dosage form, such as a tablet, capsule or ampul, it will show the exact amount of each ingredient for a single dose (tablet, capsule or ampul) and for the entire number to be made. The full instructions for manufacture must appear on it with specification not only of types of apparatus to be used but also sometimes the exact piece of equipment.

One of the important functions of the control department at this stage of the proceedings is to be sure that the standard instructions are complete, accurate in detail but not verbose, and are so clearly stated that there is no likelihood of misunderstanding. This does not mean that control men should write them, for this job may be done more easily and effectively by the men who have conducted research and developmental work on the product. But the control department must be sure that the instructions include every pertinent detail and are stated with such clarity as not to be ambiguous or confusing.

The master formula will also provide spaces, duly indicated, for recording all work done and the signatures of those doing it, including all tests, assays, inspections, etc. Part of this master formula will be master tickets or orders for each ingredient to be supplied from the general stock to the manufacturing department for this specific product.

Another rule, which should be strictly observed, is that no change in a manufacturing formula or instructions may be made without the approval of the control department, and that any approved change must actually be made by the control department. This does not in any way question the scientific ability or good sense of the manufacturing or research staff but simply places certain responsibilities where they belong so there can be no confusion. Almost always such changes will be made on recommendation initiated by the research or manufacturing staff, but once a formula is established it should never be changed in the slightest except by and with the consent of the control department.

Manufacturing Operations

The beginning of manufacture is the issuance of a manufacturing formula for some directed amount of the product desired. This, with its ingredient tickets or orders, is an exact reproduction of the master formula. When issued it is given a serial number identifying it permanently in all future records. The title used is that which will be subsequently used on the label. As each manufacturing card is issued it is listed in numerical order with the name and amount on sheets suitable for use in a loose leaf binder. These sheets are duplicated for records wherever such lists may be of service.

The material or ingredient tickets then go to

the point at which records of available material are kept and notation is made on them of the particular lot from which the desired material is to be taken. This is then weighed or measured out into suitable transfer containers or supplied in original packages in the specified amount. The amount is verified by the dispenser if in original packages. The quantity is next checked for weight or measure by another man, and a third man checks the identity and the receiving or manufacturing number of the material dispensed.

The ingredients now go to the department where actual manufacture will proceed. All the materials are assembled at one place and each again is checked for weight or measure by an employee of that department. The identity and number of each ingredient is again verified by a different man.

The actual manufacturing operation now begins. Each item is used according to instructions on the formula card, the operation being checked by a supervisory member of the department. As each item is used it is checked off on the formula card and its identifying number entered thereon. At the same time each step of the operation is likewise checked off. During manufacturing operations and at their conclusion a wide variety of tests by chemical, physical or physiologic means may be required. These will be discussed later. A control inspector in the department approves the finished product and its card record. It is then approved and the record signed by the department manager. Next, the card and a representative sample of the completed product go to the chief control inspector, working in the office of the director of control, who examines the sample and the entire record of production and tests. If all is in order final approval is given to the lot. Not until this is done is it permissible to proceed with any packaging operation.

A Cardinal Principle

At this point special emphasis must be given to a cardinal principle of manufacturing control: At every stage of operations an appropriate label, identifying the material being used or the product being made, *must* be in plain sight on every container and every piece of apparatus employed of whatever character it may be.

The samples are kept for reference for a number of years. The time will vary with different laboratories and should be not less than three years and preferably at least five years. The time during which the manufacturing card records are kept will also vary in different laboratories, but in the one with which the writer is associated they are kept permanently. Given a formula number, the corresponding card record can be located for any lot of any drug made for more than sixty years past.

It seems appropriate at this point to attempt a brief survey of some types of methods of scientific control and a few of their interesting special applications, illustrative of what may be done in this field.

Control Tests and Their Application

Since in this series of papers our thoughts are directed primarily to the development of new drugs it is worth while to set down here a tabulation of some of the things for which control tests may be required. No single product will need all of them, so it is just a reminder list of types of test which are not to be overlooked if required. Neither is the list so comprehensive that some special product may not require a specific test beyond those mentioned here in this general manner.

1. *Physical properties*
   - Color, odor, taste, appearance
   - Solubility—in water, other solvents
   - Specific gravity
   - Melting point
   - Optical rotation
   - Refractive index
   - Viscosity
   - Surface tension
   - *p*H (hydrogen ion concentration)
   - Visual and absorption spectra
   - Ultraviolet radiation effects, fluorescence
   - Effect of light, heat, cold, exposure to air
   - Volatility, inflammability
   - Special or unusual characteristics
2. *Identity tests*
3. *Purity tests* (qualitative or limiting)
   - Nature of possible impurities
   - Necessity for limits
   - Special tests so required
   - General tests; for example, heavy metals, especially arsenic, lead, mercury, copper or any other detrimental to the finished product
4. *Biologic tests*
   - Safety or toxicity
   - Sterility and pyrogens
   - Potency

5. *Assays*

   Active constituents
   Moisture, volatile matter
   Ash

6. *Packaging*

   Stability
   Reaction with materials of container

Methods in detail for applying many of the above indicated controls are to be found in the U. S. P. and N. F. It is often not realized that, in addition to the tests given in the individual monographs of these compendia, much more is necessary to assemble full descriptions of, and data regarding, test procedures.

In National Formulary VIII, about 220 pages are devoted to such information, and in the U. S. Pharmacopœia XIII nearly 300 pages are required for the same purpose. For example, N. F. VIII says under Sodium Phosphate Solution that it "meets the requirements of the test for Arsenic, page 689," and on turning to that page we find two full pages devoted to description of the test. Again in U. S. P. XIII the monograph on Oleovitamin A and D covers less than a page, and regarding the assay says, "Proceed as directed under Vitamins A and D Assays," and on turning to this we find the complete description covers over seven pages. When it is remembered how many ingredients used and how many preparations made by pharmaceutical manufacturers do not appear in either of these volumes it is not surprising that the accumulated control data for which they have need are almost encyclopedic in quantity.

A very few illustrations of the use of some types of tests listed above may be of interest:

Melting point—This is one of the most valuable criteria of purity for a large number of organic substances and a material aid in identification. Slight traces of impurities may have a pronounced effect by lowering the melting point. By use of special heated microscope stages it is possible to determine melting points with almost invisible quantities. The melting point readily distinguishes chlorobutanol containing traces of water from that which is anhydrous. A peculiar double melting or congealing point is a characteristic of synthetic menthol.

Optical rotation may be a distinguishing characteristic of many substances and an evidence of identity and purity. It is a peculiar fact that substances which give identical chemical reactions may have exactly opposite optical rotation in solution and differ tremendously in physiologic activity. For example epinephrine in the dextrorotatory form is only about one-fifteenth as active as the laevorotatory form. Determination of optical rotation is the easiest and simplest means of assaying simple dextrose solutions.

Refractive index of volatile oils is one of the best means for proving the absence of adulterants, which in most cases would appreciably change this factor if present.

Viscosity is a very useful indication of the suitability of liquid petrolatum for internal medication. The viscosity of solutions of gums, such as acacia and tragacanth, is valuable evidence of their usefulness for making emulsions.

The determination of *surface tension* of liquids has been a helpful test in the most modern study of disinfectants or germicides for topical application, and becomes in some cases a necessary control test.

pH value, or hydrogen ion concentration—This extremely accurate means for determining minute differences in the acidity or alkalinity of solutions has had its greatest practical development during the past twenty-five years. The principle was enunciated much earlier but its practical applications were slow. Not until about ten years ago were such tests placed in the U. S. P. and N. F., although they had been used in many scientific laboratories for a much longer time. A discussion of the method of test is out of place here, as its meaning and use are well described in the scientific literature. Suffice it to say that without this potent tool of the control laboratory the production of such things as insulin, liver extract and many of the hormones would be almost impossible. This test is also a necessity in the preparation of all manner of solutions for parenteral injection.

Spectrographic tests and methods of assay are being more and more widely used. They range from the simple qualitative tests for lithium or barium, which every science student has seen, to the estimation of vitamin D in oils by its absorption spectrum, or the examination of the estrogenic hormones by similar means.

It is needless to amplify comments by a recital of tests or enumeration of assays. These will serve as types of technical control methods. We will pass on to the last step before a medicinal product is ready for use, namely the packaging.

Packaging Control

Packaging will require, among other things, a knowledge of possible reactions between the material of the container and the drug, of the conditions that will promote stability or tend to

cause deterioration, and the devising of tests for maintenance of optimum conditions.

Among such control tests will be those for the quality of the glass of bottles or ampuls, such as those given in detail in the U. S. P. and N. F.; the character of closures whether cork, rubber, metal, plastic or various compositions; the purity of nitrogen or carbon dioxide if these are used to displace air in the containers; and even the kind of cement or glue that fastens the liner to the inside of a bottle cap.

Control checks are, of course, required for weight, measure or count of the amounts placed in individual packages, similar to those already described under manufacturing operations. Inspection of the packages will be made after filling and before labeling. In the case of ampuls or vials of solutions for parenteral injection the inspection at this stage of production is one of the most troublesome and exacting of any in the whole range of physical examinations. The difficulty is twofold. First, what is the correct interpretation of the phrase "substantially free" as used in both the U. S. P. and N. F. in describing the clarity of such solutions, and how can this best be determined?

So far this has been accomplished by critical visual inspection under conditions similar to those indicated by both the U. S. P. and N. F., but a comprehensive research program under the auspices of a considerable group of members of the American Drug Manufacturers Association is now in progress. This, it is hoped, will result in the development of an electronically operated mechanism giving accurate and unvarying results in such inspections. It is too early in the work as yet to draw positive conclusions, though prospects appear good.

The chain of control procedures ends at the finishing or control number applied to the package labels. This is the key to all the preceding records of purchase, manufacture, test and packaging, from the purchase of ingredients to the application of labels and wrappings. It may be either the manufacturing or formula number, continued in use to this stage of proceedings, or it may be a separate finishing number, the use of which begins at the point where actual manufacture of the medicinal preparation is completed and any packaging and labeling operations begin. There are good arguments in favor of either procedure, but the latter possesses certain advantages.

Here ends that chain of faith referred to in an early paragraph. These are the materials from which the maker of medicines must forge the anchor for this chain.

FRANK O. TAYLOR, author of "Quality Control," was chief chemist for Parke, Davis and Co. for 21 years and a member of the firm's staff since 1902. He retired in 1945, but continues in a consultant capacity. A graduate pharmacist from the Cincinnati College of Pharmacy, Dr. Taylor maintains an active interest in pharmaceutical affairs. He is a life member of the American Pharmaceutical Association and has served as first vice-president and as a member of the Committee on Laboratory. He is chairman of the Contact Committee of the American Drug Manufacturers Association, and has been a member of the Committee since its inception in 1924. Long active in the American Chemical Society, Dr. Taylor has served as chairman of its Division of Medicinal Products and as chairman of the Detroit Section. He has also been chairman of the Scientific Section of the American Drug Manufacturers Association. He has made many contributions to the field of drug standards and is a member of the U. S. Pharmacopoeia Revision Committee.

BIOLOGICALS

[PUBLIC LAW 410—78TH CONGRESS]
[CHAPTER 373—2D SESSION]
[H. R. 4624]

AN ACT

To consolidate and revise the laws relating to the Public Health Service, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

TITLE I—SHORT TITLE AND DEFINITIONS

SHORT TITLE

SECTION 1. Titles I to V, inclusive, of this Act may be cited as the "Public Health Service Act".

DEFINITIONS

SEC. 2. When used in this Act—

(a) The term "Service" means the Publi

(b) The term "Surgeon General" mea
the Public Health Service;

(c) The term "Administrator" means
istrator;

(d) The term "regulations" means the Surg
rules and regulations made by the Surg

of the Administrator;

(e) The term "executive departme
ment, agency, or independent establi
any corporation wholly owned by the

(f) The term "State" means a St
Hawaii, Alaska, Puerto Rico, or t
used in section 361 (d) such ter
Columbia, or Alaska;

(g) The term "possession" i
Puerto Rico and the Virgin Islan

(h) The term "seamen" inclu

(i) The terms "navigable ...

717, SEVENTY-FIFTH CONGRESS,
ER 675, THIRD SESSION, S. 5

AN ACT

ment in interstate commerce of adulterated and
s, devices, and cosmetics, and for other purposes.

by the Senate and House of Representatives of the States of America in Congress assembled,

CHAPTER I. SHORT TITLE

SECTION 1. This Act may be cited as the Federal Food, Drug, and Cosmetic Act.

General Regulation. [§ 2.1] (a) The provisions of regulations promulgated under the Act with respect to the doing of any act shall be applicable also to the causing of such act to be done.

(b) The definitions and interpretations of terms contained in section 201 of the Act shall be applicable also to such terms when used in regulations promulgated under the Act.

CHAPTER II. DEFINITIONS

SEC. 201. For the purposes of this Act—

(a) The term "Territory" means any Territory or possession of the United States, including the District of Columbia and excluding the Canal Zone.

(b) The term "interstate commerce" means (1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other T
not organized with a legislative body.

(c) The term "Agency" means the Fed
istrator.

(d) The term "Administrator" means the

(e) The ...

DRUGS

Federal Regulation

I—FOOD AND DRUG ADMINISTRATION

by ROBERT P. HERWICK*

THE Federal Food, Drug and Cosmetic Act provides, among other things, that no person shall introduce or deliver for introduction into interstate commerce any *new drug* unless an application filed with the Administrator of the Federal Security Agency is effective with respect to such drug.

This section of the statute became effective on June 25, 1938, and to date over 6100 new drug applications have been submitted to the Administrator for consideration. Of these 6100 applications, more than 4000 have been made effective, approximately 1300 remain incomplete and 373 have been withdrawn voluntarily by the applicants. The remaining applications are either under consideration at the present time or orders refusing to permit them to become effective have been issued.

It is surprising that up to this time we have not had an appellate court decision involving new drugs. Consequently, our discussion of this subject represents an administrative interpretation of the Act based on eight and a half years' experience. But before proceeding to discuss the administrative evaluation of the safety of new drugs, we should give consideration to the statutory background of this subject.

Section 201(p) defines a new drug as:

> (1) Any drug the composition of which is such that [it] is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling.
> (2) Any drug the composition of which is such that [it], as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

If one examines carefully the two parts of this definition, it can readily be seen that the first part deals with the ordinary concept of a new drug, and the second part provides that a drug which becomes generally recognized by experts as safe continues to be a new drug for an indefinite period. This latter provision is the basis for requiring the filing of new drug applications by all manufacturers or distributors placing identical new products on the market.

A regulation under the statute excludes from the requirements of the new drug section the products which are licensed under the Virus, Serum and Toxin Act (Public Health Service Act of 1944). Regulation of drugs in this category is under the jurisdiction of the U. S. Public Health Service as described elsewhere in this issue.

Once a given product is found to fall within the statutory definition of a *new drug*, each applicant must submit in duplicate certain information as a part of the application to show that the drug is safe under the conditions of use. Let us consider briefly the information required under section 505 of the Act.

Section 505(b)(1) requires the submission of full reports of investigations that have been made to show whether or not such drug is safe for use. The Food and Drug Administration cannot undertake to outline in detail the nature and amount of investigational work that may be required to establish the safety of a particular new drug, as such investigations will necessarily depend upon the nature of the drug and the facts developed during the preliminary investigations. In the *Journal of the American Medical Association* for December 9, 1944, we have attempted to outline generally the laboratory and clinical studies that may be necessary for the evaluation of the safety of certain new drugs.† It may be stated that pharmacological and pathological studies should include several species of animals for both acute

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† A reprint of this article is available on request from the Food and Drug Administration, Drug Division, Washington 25, D. C.

and chronic toxicity. Clinical investigations should include studies by several investigators and should include information regarding the number of individuals to whom the drug was administered, the dose given, the condition treated, the frequency and duration of administration, and particularly the observations of the clinical and laboratory tests that were made to determine whether or not the individuals had been injured by the preparation.

Evidence Must Be Convincing

All such studies should be performed by experts qualified by scientific training and experience to investigate the safety of drugs. In considering the safety of a drug, the submission of reports of a few well performed studies will greatly outweigh voluminous reports of uncontrolled investigations.

Section 505(b)(2) and (3) require full information regarding the identity and composition of each ingredient of a new drug. The identification of ingredients by trade names or by vague terms—as for example "Mash-Nic," "Aerosol O.T." and "Perfume Oil"—is not sufficient to fulfill the requirements of this section. All such information should be given in detail.

Section 505(b)(4) requires the submission of a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug to insure its identity, strength and purity. The appraisal of any control system necessarily involves consideration of the products that a given manufacturer makes, the number of drugs that he handles, the physical equipment necessary for production, and many other factors.

In other words, a manufacturer who makes tablets from a single active ingredient and who has no other drugs on his premises would not need much control to prevent contamination with other drugs. However, if a manufacturer makes numerous products, a more elaborate control system is essential.

In our judgment there are certain common denominators in the establishment of an effective control system. These may be briefly stated as: (1) adequate mechanical control and (2) adequate chemical control. Adequate mechanical control involves simply a determination of the composition of the materials which enter into the manufacture of a tablet, solution or other dose form, a record of the amount used, and finally a record of the number of finished tablets, etc. With minor variations, the weight or volume of the finished product should correspond with that of the raw materials. Chemical control involves sampling operations at various stages of manufacture, beginning with the raw materials and ending with the final product. Many drug firms have devised elaborate control systems which go far beyond this simple outline. In general, those that have devised the best control systems readily agree that there is no system yet devised which cannot be still further improved.

Section 505(b)(5) requires the submission of such samples of such drug and of the articles used as components thereof as the Administrator may require. Numerous applications that are submitted deal with situations in which it is not practical to submit a complete unit or package of the drug with the application. If it is the applicant's desire to submit a new drug application without including a sample of the drug, this may be done. If the sample is essential to the consideration of the application, he will be advised of that fact.

Section 505(b)(6) requires submission of specimens of the labeling proposed to be used for such drug. This should include not only all labeling which is to accompany the market package, but all descriptive circulars or brochures for such product. It is not necessary initially that the labeling be submitted in printed form, but final printed copies of all labeling and promotional material must be submitted as a part of the file for the product.

A Prediction of Safety

In the handling of new drug applications we are called upon to predict, before a new drug is placed on the market, whether or not it is going to be safe for use. The industry and ingenuity of many chemists in developing new products make this a particularly important responsibility. The safety data submitted by the biochemist, the bacteriologist, the pharmacologist and toxicologist, the clinician and others must be correlated and evaluated as quickly as possible. This is an activity unique among the activities of the Food and Drug Administration relating to drugs, in that it is the only drug section which provides for the issuance of licenses or permits for drugs that have not been previously recognized by experts as safe for use. Under other provisions of the statute we are responsible for the certification of batches of insulin and penicillin that are considered safe and efficacious for use.

In administering this quasi-licensing new drug

provision of the statute, there is placed on the Administrator the serious responsibility of determining—from the material submitted with respect to the effects of a drug, its composition and its manufacturing controls—that the drug is or is not safe. Further, he has the responsibility of rapidly and efficiently releasing safe and effective new drugs for use, as well as giving equal treatment to individuals submitting applications for identical or similar drugs. We recognize these facts and are making every effort to carry out the purpose and principle of this section in a creditable manner.

The question "What are the criteria of safety of a drug?" does not always find an easy answer. "Safety," as applied to drugs, is a relative term. It is a matter of common knowledge that many of our most important drugs have potentialities for injury as well as for benefit and that in therapeutic doses drugs may manifest some degree of adverse effect as well as beneficial effect. The provisions of the Act place upon the applicant the duty of demonstrating by adequate investigations that the drug, under the conditions of use, has greater potentialities for good than for harm.

The law does not leave to the realm of doubt that which can be demonstrated by scientific facts. Applicants are expected to make use of all reasonable means of investigation. The goal should be a demonstration of the safety of the drug, not merely the accumulation of data through superficial investigations which the applicant hopes will be sufficient to secure the effectiveness of the application.

When it can reasonably be concluded that—under the conditions prescribed, recommended, or suggested in the proposed labeling—the potentiality of a drug for harm is negligible or minor, and that its probable benefit is clearly sufficient to justify its use notwithstanding possible adverse effect, the drug is safe within the meaning of the statute. But if it is concluded that the potentiality for harm is not clearly outweighed by its probable benefit, the drug may not be safe within the meaning of the statute.

For example, sulfathiazole was recognized at the time the application was permitted to become effective as safe for use by physicians for the treatment of pneumonia and other disease conditions irrespective of certain toxic manifestations which accompany its use. When used for the treatment of these diseases its beneficial therapeutic effects clearly outweigh its toxic effects. However, sulfathiazole would not be recognized as safe for the treatment of tuberculosis or tularemia, where its therapeutic efficacy is nil.

In addition to the recognition of sulfathiazole as safe for use in the treatment of pneumonia, among other disease conditions it is recognized as safe for the treatment of gonorrhea under continuous medical supervision. However, because of the inability of laymen to recognize or properly treat many of the toxic manifestations of the drug that are incident to its use, it has not been considered as safe for over-the-counter sale.

It should be pointed out that the Act does not permit us to set ourselves up as a board of experts in the field of therapeutics to judge the relative efficacy of a given product in comparison with other drugs of the same class and, by grading, attempt to deny an effective application for a product solely because its efficacy is not as great as that of other drugs in the same class. At the present time, we must depend on the Council on Pharmacy and Chemistry of the American Medical Association for such an evaluation.

In arriving at a decision regarding the safety of new drugs, there is many times a diversity of opinion among experts investigating the drug. In such instances it is necessary for our medical officers to obtain facts from the experts by personal discussions of our problems. On certain occasions it is important that we consult with other specialized groups in the medical profession to obtain the best information available regarding the new product. Among such groups are: (1) The Council on Pharmacy and Chemistry of the American Medical Association; (2) American Diabetes Association; (3) American Academy of Allergists; (4) American Academy of Pediatrics; and (5) American Dermatological Society.

Every effort is made to obtain the best available factual information regarding the new product. Once detailed data are obtained they are carefully weighed by us and a decision is reached regarding medical consensus among experts as to the safety of the drug.

In addition to these primary considerations of the safety of new drugs we must examine certain provisions of the statute before deciding whether or not an application may be made effective.

Section 502(f)(1) requires that:

> ***the labeling of drugs bear "adequate directions for use***", but further provides for an exemption from this clause if the drug cannot be used safely and efficaciously except under medical supervision.

Section 502(f)(2) requires:

> "***such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users***."

Therefore it can be seen that in the study of the safety of new drugs we must reach a decision as to whether or not the product is safe for use under directions for lay use or if it is safe only on physician's prescription. And in addition we must contemplate such adequate warnings as are necessary for the protection of the users.

In the final study of new drugs the Food and Drug Administration must give weight not only to the data submitted by the applicant regarding the safety of the product; to the opinions of experts; to the need for warnings; to the safety under the conditions of sale; but also to the statutory provisions for denying an application if we are of the opinion that the product should not be approved. Applications for new drugs may be denied for the following reasons [Sec. 505 (d)]:

(1) "the investigations, reports of which are required to be submitted to the Administrator, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use***;
(2) "the results of such tests show that the drug is unsafe for use or do not show that such drug is safe for use under the conditions of use;
(3) "the methods used in and the facilities and controls used for the manufacture, processing, and packaging of such drug are inadequate to preserve its identity, strength, quality, and purity;
(4) "upon the basis of the information submitted as a part of the application, or upon the basis of any other information before the Administrator, he has insufficient information to determine whether such drug is safe for use."

Thus, if all of these statutory provisions are carefully studied, together with the material submitted by the applicant and other information available, it will be seen that we must give consideration to many factors in approving or denying new drug applications. Some of these are:

1. What are the scientific criteria for approval of new drugs?
2. What is the medical consensus among experts as to the safety of the product under the proposed conditions of use?
3. Is the drug safe for use under directions for over-the-counter sale or for use only on physician's prescription?
4. Have adequate warnings been placed in the labelings to secure safety of a drug new to the lay public or to the medical profession?
5. What are the statutory provisions for refusal of an application?

One should remember that all data must be considered within the compass of the entire statute. The law and scientific information must meet on common ground.

This is a difficult task, and our entire staff—including administrative officers, medical officers, chemists, bacteriologists, pharmacologists, immunologists, nutritionists and others—must review the information submitted and consult with other specialized groups to obtain the necessary background for the approval of important new drugs. When final consideration has been given to all of the material obtained, we believe we have a real, tangible, factual basis for approval or denial of new drug applications.

The pharmacist who is ultimately responsible for the distribution of new drugs can examine the label of the product for a determination of how it is to be dispensed. If it is labeled with the caution, "To be dispensed only by or on the prescription of a physician," he must dispense the drug only on physician's prescription; if its labeling bears adequate directions for lay use he may dispense it over the counter.

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FEDERAL REGULATION . . .

II—U. S. PUBLIC HEALTH SERVICE

by M. V. VELDEE*

THE introduction of a new product comes under the control of the Federal biologics law† if it is a virus, therapeutic serum, toxin, antitoxin, or an analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenical), and if it is applicable to the prevention, treatment or cure of diseases or injuries of man. The law applies only if a product is offered for sale, barter or exchange in interstate commerce, or in the District of Columbia, or for export or import sale.

Although we are interested here primarily in the development and introduction of new drugs, it should be pointed out that the biologics law does not make specific provision for the development of a new biologic. Its provisions apply equally to "old" and to "new" products. A product license cannot be obtained until requirements, which will be discussed later, have been met. The product cannot be sold until it has been licensed. Therefore little more is needed to assure adequate developmental work before a product is made available for use. It has always been the belief of those at the National Institute of Health who are responsible for enforcing the law, that the licensing system is adequate for this purpose.

Unless an establishment holds an unsuspended unrevoked license authorizing the propagation, manufacture and preparation of one or more of the products within the scope of the biologics law, it may not engage in such activities. Drug products in other categories fall within the scope of the Food, Drug and Cosmetic Act, which is enforced by the Food and Drug Administration and discussed elsewhere in this issue.

In the case of the biologics law, enforcement has been made a responsibility of the U. S. Public Health Service. The actual administrative details are assigned to the Biologics Control Unit of the National Institute of Health. The Unit is responsible to the Surgeon General of the Public Health Service through the Director of the Institute.

The administrative responsibility rests in the Administrator of the Federal Security Agency, of which the Public Health Service is a part. Regulations having to do with administration are made by the Surgeon General of the Public health Service with the approval of the Administrator.

On the other hand, the biologics law specifies that regulations covering standards designed to assure the continued safety, purity and potency of such products shall be made jointly by the Surgeon General of the Army, the Surgeon General of the Navy and the Surgeon General of the Public Health Service, and approved by the Administrator.

What are the individual products which come within the scope of the statute? As used in the law, the word "virus" is defined by regulation to include any product containing the minute living cause of an infectious disease. The terms "therapeutic serum," "toxin" and "antitoxin" will be well understood by the reader and need no further definition in this discussion. The term "an analogous product" is a more vague designation and, therefore, is defined in detail in the regulations. The definitions used are as follows:

(a) "A product is analogous to a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(b) "A product is analogous to a therapeutic serum if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum and intended for administration by a route other than ingestion.

(c) "A product is analogous to a toxin or antitoxin if intended, irrespective of its source of origin, for the prevention, treatment, or cure of diseases or injuries of man through specific immunization."

At the time of the first World War it became urgently necessary to manufacture the arsphenamines in this country since the German supply, which was the only one available, had been cut off. To avoid delay in setting up control measures the Congress specified that arsphenamine and its derivatives should be controlled by the Public Health Service in the same way as the biologic products. This provided prompt and adequate

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† The law now in effect is known as Public Law 410 — 78th Congress, and more specifically as Public Health Service Act, July 1, 1944. As far as the section of the Act dealing with biologics is concerned, it represents a re-enactment of the original biologics law that was enacted as of July 1, 1902. Regulations prescribed under the 1944 statute appear in the *Federal Register* for January 21, 1947, page 411.

control over a group of products that are difficult to manufacture and potentially dangerous to use. Later the law was broadened to include any other trivalent organic arsenic compound.

To complete the definition of scope it has been necessary to define in the regulations the word "applicable" as it is used in the law. This is covered by the following wording:

> "A product is deemed applicable to the prevention, treatment or cure of diseases or injuries of man, irrespective of the mode of administration or application recommended, including use when intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person; and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biologic product."

Operation of the Law

The law functions primarily through a license system in that it requires an establishment wishing to engage in the operations described in the foregoing discussion to hold an unsuspended and unrevoked license issued by the Administrator of the Federal Security Agency. This is known as the "establishment license." In addition, a similar license is issued for each specific product and this is known as the "product license." To obtain these licenses the law specifies certain requirements which must be met. These may be summarized as follows:

(a) Certain labeling items must appear on each package.

(b) The package must not be falsely labeled.

(c) The establishment may be inspected by duly qualified persons whenever considered necessary.

(d) License may be issued only upon a showing that the establishment and the product for which a license is desired meet standards designed to insure the continued safety, purity, and potency of such products, prescribed in regulations made jointly by the Surgeon General of the Public Health Service, the Surgeon General of the Army, and the Surgeon General of the Navy, and approved by the Administrator, and licenses for new products may be issued only upon a showing that they meet such standards.

The Biologic Regulations

In the first instance the regulations provide those administrative details having to do with the issuance of license, inspection of the establishment, and such other related factors as need to be specified. For example, an establishment may be licensed only after inspection and the determination that its location and physical equipment are considered adequate for the purpose intended. The management and the scientific staff involved in production are interviewed and an attempt is made to judge each one's qualifications as related to the problem at hand. The prospective manufacturer must demonstrate his ability to manufacture at least one licensable product before an establishment license can be recommended.

In the second instance the regulations spell out all those details which the three Surgeons General and their advisers believe are necessary to assure the continued safety, purity and potency of each product for which a license is desired. A product license may not be issued except to an establishment that qualifies for an establishment license. The main regulations state those requirements that are applicable to all licensed products.

To define the expiration date of each product in relation to the recommended storage temperature a supplement to the general regulations is issued which is known as the "Dating Decisions." As the title indicates, this gives information on the dating of each product and its relation to the date of manufacture and the storage temperature both before and after the date of issue.

Minimum Requirements Provided

Finally, most products have characteristics as to production, potency testing and stability that vary with each product. To present these adequately in sufficient detail there is provided a set of minimum requirements for each product. These expand the standards mentioned in the general regulations which are necessary to assure safety, purity and potency.

Safety is interpreted to apply to the relative freedom from harmful effect to the patient when a product is prudently administered, taking into consideration the character of the product in relation to the condition of the patient at the time. The principal factor is sterility. Because of the nature of most biologic products, this can only be a relative matter in relation to the volume of the dose. Other factors of safety are the degree of freedom from pyrogenic substances, the degree of detoxification of some products, the composition of the medium containing the active ingredients (particularly in relation to allergy) and the suitability of the package for the preservation and administration of the product.

Purity is interpreted to mean the degree of freedom from extraneous matter—whether harmful to the patient, deleterious to the product or

otherwise—in the finished product. Biologic products for the most part are neither physically nor chemically pure products. However, the objective of the manufacturer and the National Institute of Health is in the direction of increased purity through the application of improved methods as they are developed.

Potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data. In its simplest terms this is merely to say that a product must have a useful purpose either in the prevention, treatment or cure of diseases or injuries of man. A product showing less than this cannot qualify for license.

What is to constitute acceptable and adequate evidence as to the safety, purity and potency of a new product? The regulations place the responsibility for this decision on the Surgeon General, or in the case of an appeal from his decision, on a review board of three officers appointed by the Surgeon General for that purpose. Obviously it is not the wish, or practice, of the Surgeon General to make decisions of this character in a purely arbitrary way. In practice, an effort is made to evaluate the product in relation to its ability to accomplish the prophylactic or therapeutic response which the originator claims. For some products, such as tetanus toxoid or thrombin, evidence is easily obtainable, whereas for other products it is a most difficult task.

In examining data presented to support the requirement of potency the National Institute of Health bases its evaluation on several factors. These may, at least in part, be summarized as follows:

(a) A review of the plan of study followed in developing the product.

(b) Was the study adequately controlled?

(c) By whom was it conducted?

(d) What was the investigator's connection with the future of the product or with the manufacturer?

(e) Were the investigative data accepted for publication?

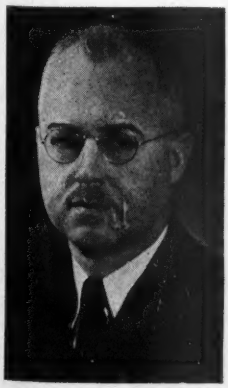
(f) What is the scientific standing of the journal in which publication is made?

(g) Were the original findings confirmed by disinterested investigators?

(h) Finally, does an independent examination of the claims for the product agree with well established scientific principles of the basic sciences involved?

Unfortunately, not all "data" are acceptable evidence. There is much in published scientific literature that remains unconfirmed and has been written in an ink of confusion and inadequacy which fades rapidly on critical reading.

Persons who may be interested in biologic products should feel free to make inquiry of the Biologics Control Laboratory, National Institute of Health, Bethesda 14, Maryland. Available literature will be supplied and as far as possible any questions will be answered. The Institute staff has always felt that it shares with the investigator and the manufacturer the responsibility for providing the public with biologics of good quality.



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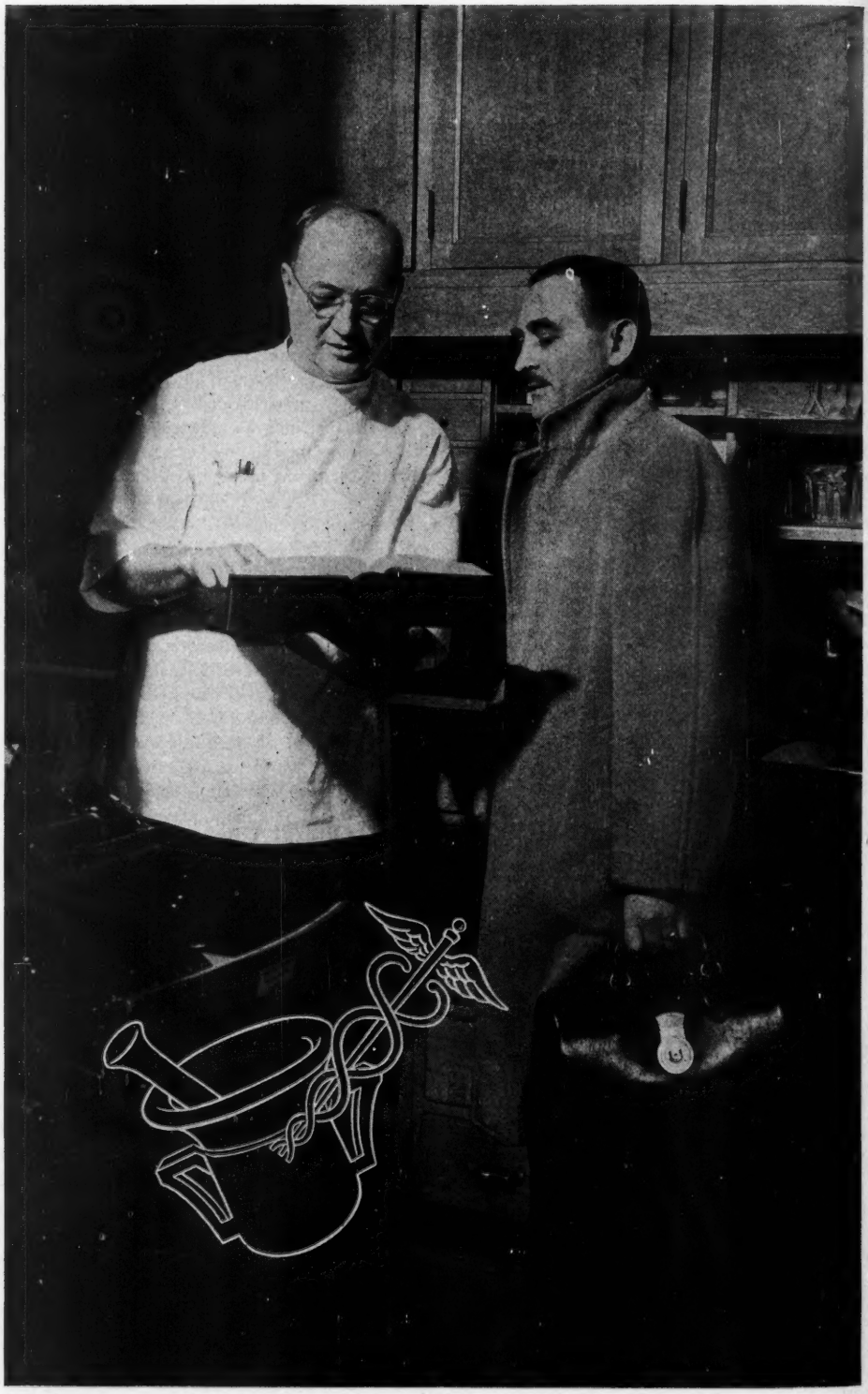

The Practicing Pharmacist

by

JAMES S. HILL*

THE practicing pharmacist is the final controlling factor in the distribution of all drugs, new or old. Whether the drug reaches the patient as a prescription or as a packaged proprietary, a large measure of responsibility for its intelligent use rests upon the pharmacist.

The American lay press has made a fetish of reporting medical and scientific news, and frequently leans toward the sensational at the expense of the accurate. That the press is responsible for making the laity better informed on health matters is without question, but its failure on frequent occasions to stress the doubtful value or dangers of new drugs makes it at least partially responsible for some misuses of new drugs. This places upon the pharmacist still greater moral responsibility to make sure that the public is fully aware of the limits of usefulness and of the potential dangers characteristic of a particular drug if used without competent medical advice.

It is common knowledge among professional people who have had experience with new drugs that their harmlessness, when put to the acid test of unrestricted public use, frequently leads to a revision of scientific views concerning them.

For example, this is true of the use of high potency vitamin-D preparations in the treatment of arthritis. Once considered harmless, it is now known that such preparations may cause deposits of calcium in certain organs and lead to fatal results both in adults and newborn infants. Therefore, the dispensing of such products is now limited to prescriptions.

The use of oily nose drops, once a common practice, was largely discontinued when knowledge of the possibility of lipoid pneumonia became available.

Think of the harm to which the public was exposed when Demerol was announced as an analgesic next to morphine in effectiveness but without danger of habit formation. Demerol today is considered a habit forming drug, and has been placed under narcotic laws.

New drugs, products of modern science, have changed the prescribing habits of the physician and buying habits of the public. No longer are they dealing with naturally occurring drugs having mild or uncertain effects, but with synthetic materials often foreign to the human body. Such drugs have definite, potent effects, and not infrequently have pernicious side actions.

The public resents any implication of lack of intelligence, particularly in the matter of drugs. This attitude is more noticeable in the so-called intelligent strata than in the group that has not enjoyed the privilege of higher education. It is difficult for the public, accustomed to innocuous drugs, to realize that legal and ethical restrictions upon the dispensing of new drugs is for their protection and not an infringement upon their age-old right to diagnose and self-prescribe.

The distribution of more specific and potent remedies has imposed legal and professional responsibilities on the pharmacist to such an extent that his professional position has been greatly strengthened. But with this has come the greatest responsibility of all, moral responsibility—man's obligation to his own kind. This obligation will be met by those pharmacists who have sufficient background and training to realize that, at least in the distribution of new drugs, the pharmacist is his brother's keeper.

Just as there are innumerable steps in the discovery, manufacture and control of new drugs, so there are many facets to the responsibility of maintaining adequate pharmaceutical service and information for the physician and his patients.

Preservation of drugs, with its newer implications, will serve as an example. Previously "preservation" was of significance only in the pharmacy. Now it is frequently applicable to the finished prescription in the patient's home. Solutions of penicillin, for instance, quickly decline in potency, even when refrigerated. Tablets and lozenges must be dispensed in air-tight containers and refrigerated. Most prescriptions are kept in the medicine chest, usually located in the bathroom. What would happen to the potency of penicillin tablets in the usual cardboard pillbox nakedly exposed to the humidity of the

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average bathroom after one or two hot showers? Another favorite place for medicine in the home is the kitchen cabinet, usually located near the cook stove. Temperatures in small, centrally heated kitchens during cooking periods may easily reach 85 to 90° F. Imagine the destructive effect of this temperature upon the expensive penicillin and vitamin preparations of today. Even cod-liver oil may be quickly turned rancid.

Antibiotics in their various dosage forms, the vitamin preparations, vaccines, and other new products, when considered in relation to preservation in the pharmacy and in the home, pose an economic problem for the retail pharmacist. The many liquid forms of vitamins in gallons and pints, and the packaged proprietary single dosage forms, would alone overflow any domestic type refrigerator. It becomes obvious that the answer to adequate refrigeration in a well-stocked pharmacy is either a large cold-room or refrigerated shelves.

One might also mention the present difficulty of obtaining, except in large quantities, amber-colored bottles necessary to protect liquid forms of vitamin preparations from the harmful effects of light. Some manufacturers prefer to market glass containers in more attractive colors than the deep amber necessary to screen the light rays that have deteriorating effects.

For some time a need has been felt for a universal dating code for pharmaceuticals understandable to all pharmacists. Many of the new drugs that are being introduced have an expiration date, but too many do not have an understandable manufacturing date. There is no convenient means of knowing how long manufactured drugs lay on the manufacturers' and wholesalers' shelves under unknown storage conditions before they are received in the pharmacy. As the majority of drugs change very little in appearance with age, the pharmacist even when conscientious, is hampered when judging their potency. Accuracy has always been considered most important in compounding, but today potency at the time of dispensing is of equal importance.

These problems of preservation are a few of the obvious changes in the professional requirements of modern pharmacy brought about by new medicinals. Less obvious to the public, but exerting a tremendous pressure on the economic structure of retail pharmacy, is the multitude of clinically unnecessary variations of a product and multiplicity of trade names for the same drug.

The drugstore whose policy, sometimes of necessity, has been to use most capital to provide fast-moving side lines, often will be in a position where even a representative stock may not be provided to meet the orthodox health needs of the community. The public is turning for its pharmaceutical needs to those pharmacies that have invested most of their capital in health needs and have specialized in this field. This subconscious professional recognition by the public is very slowly splitting the structure of retail pharmacy. Two types of establishments are emerging: those required to supply health needs only occasionally, and those whose facilities are constantly employed to answer the calls for professional assistance.

Continuing Interest in Education

At the last meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION, the interest of pharmacists in modern improvements in pharmaceutical education was obvious. They also were interested in extended education for themselves. It is unusual for retail pharmacists to take an active interest in the formal education of students. However, the influx of complex and potent preparations has taxed the mental equipment of the pharmacist, even though the physical equipment of his pharmacy for compounding may be used less frequently. He has come to realize that a broader background is necessary to relieve him of this burden. Not so long ago the practicing pharmacist's part in the introduction of new drugs was less significant. The complexity and potency of the newer drugs now gives him added responsibilities. The pharmacist today is expected by the medical profession and the manufacturers to be the impartial interpreter of new drugs. In other words, he must be a professional consultant.

As a professional consultant the pharmacist is expected to interpret new drugs in relation to the fundamental sciences required in their production. How can we explain the difference in activity between Benzedrine sulfate and Dexedrine sulfate if we do not know something about the chemistry of these sympathomimetic agents? It should be recognized that the type of synthetic reaction employed produces a racemic mixture, amphetamine (Benzedrine). Of the *d*- and *l*-isomers present, the former is more potent, particularly as a central nervous system stimulant. The dextrorotatory isomer (Dexedrine) therefore provides a product of greater psychomotor activity and less pressor effect than the racemic mixture (Benzedrine).

How can we evaluate the proprietary protein

hydrolysate if we do not understand the biochemistry of the amino acids and methods of production as well as the meaning of their analyses? A protein hydrolysate, in the light of present knowledge, must contain at least 8 or preferably the 10 essential amino acids. These should be in their natural form, as many amino acids are only partially utilized by the body when racemic. The potency of hydrolysates may be compared and partially evaluated by the use of the Alpha Amino N÷Total Protein N ratio, and consideration of total protein content. Acid hydrolysis often destroys tryptophane and so such a product must have tryptophane added to meet the first requirement of a good hydrolysate.

Questions concerning the origin, effectiveness, speed of protection and local effect of influenza virus vaccine "A" and "B" are prevalent at this time. Since little specifically is known about the effectiveness and duration of protection, such questions must be answered in the light of related vaccines. Until we have a mild or severe epidemic of influenza such questions cannot be answered authoritatively except in theory.

Keeping Pace with Clinical Progress

An understanding of the toxicology and clinical effect of new drugs is required to answer the physician's inquiries concerning proper dosage. Naturally side effects are very important and may even bar the use of an otherwise valuable drug.

It is advantageous in the study of a new drug to be aware of its experimental development before its introduction. Such journals as the *Journal of the American Medical Association*, the *Journal of Pharmacology and Experimental Therapeutics* and the *Journal of Laboratory and Clinical Medicine* will usually indicate the birth of a new experimental drug. This provides a background of independent evaluation in the event a new drug is marketed. It is valuable for an impartial evaluation to temper the enthusiasm of some manufacturers and their salesmen. The pharmacist providing additional data, with authority and reference, beyond that supplied by the producer is soon recognized by physicians for his worth.

Clinical data may be obtained from local hospital staffs and internists, the *Journal of the American Medical Association*, *Medical Clinics of North America* and other journals, and from local or community seminars conducted by the medical profession and in a few cases by interprofessional groups. We consider attendance at such inter-professional meetings most helpful.

Today, with information having been deleted from the labeling of prescription drugs and the direct-mail literature to the physician so profuse that an extra filing secretary seems practically a necessity, the pharmacist is welcomed as a source of even routine information. Gutman's "Modern Drug Encyclopedia and Therapeutic Guide" and "New and Nonofficial Remedies" are important aids to answering such routine questions. When duplications of remedies occur, it should be the practice of the pharmacist to segregate them into similar or dissimilar groups and interpret them in the light of group information, stressing advantages and disadvantages wherever they may occur. The economic factor should be considered when it does not conflict with the clinical results. Where duplications occur, and no advantage is gained, we feel that the original manufacturer should be favored.

The complexity, duplication and sometimes the scarcity of these potent preparations has led the physician to seek assistance in their application and evaluation. Such assistance must for the most part be impartial, disinterested and scientific. It was only natural that the medical practitioner should turn to pharmacy for such assistance and the new field of professional consultant be opened to qualified pharmacists.

Much has been written during the preceding year listing the various periodicals and technical books a pharmacy should have to be up to date and able to answer the questions of physicians. The basic volumes for a well-balanced reference shelf were listed in the February, 1946, issue of THIS JOURNAL (7: 68, 1946), while a more extensive listing including periodicals was published by Ireland in the May issue (7: 223, 1946).

Information Files on New Drugs

Several years ago we started a file index of newer drugs, but experience showed that pharmacists first consulted Gutman's "Drug Encyclopedia," using the file only when a physician wanted some literature mailed to his office or the drug had not yet appeared in Gutman. Today a file is kept for new drug literature with several pieces of literature on each drug. If the drug has been introduced within six months, the latest clinical data are made available to physicians from the medical literature, such as the *Journal of the A. M. A.* and Saunder's *Medical Clinics of North America*, or as summarized in professional pharmaceutical publications.

To abstract the immense amount of clinical

data on new drugs today not only takes a great deal of time but also requires a pharmacy to have someone on the staff interested in medical reading. We are fortunate in having such a pharmacist, who has become our chief abstractor, with the other pharmacists acting as assistants to share the volume of reading necessary.

When an inquiry comes in from a physician on a newer drug, a record is kept of the call. If further research is necessary to answer the question adequately, these data are recorded for future reference and are discussed among all the pharmacists in either spare moments or at round-table discussions outside of working hours.

In a three months' survey, we found that physicians called us 3.7 times a day asking for professional advice on newer drugs. Certainly the pharmacist should act as a professional consultant for the medical profession when called on. The added work and expense is considerable, but the professional service is appreciated.

Newer drugs have changed the method of checking incompatibilities. In the years gone by, official preparations were used in a higher percentage of prescriptions than today. The use of varied proprietaries changes so rapidly at the whim of the physician that it is difficult for any textbook to treat the subject adequately. This leaves the investigation of incompatibilities largely up to the practicing pharmacist. Previously, incompatibilities were mostly of a single chemical or physicial type. Today we are frequently concerned with colloidal changes and interrupted *p*H systems. This necessitates equipment not formerly thought necessary in a pharmacy. We have found that a potentiometer is very helpful. The increased number of complicated proprietaries has increased incompatibility problems.

It is generally believed that the amount of compounding done in the pharmacy has sharply decreased. Some even believe this has reached a level detrimental to professional practice. There are some indications that official specifications and compounded prescriptions have not decreased so greatly in numbers as in percentage. In other words, the new medications are responsible for an increased total number of prescriptions filled.

New medications have affected the structure of pharmacy, resulted in changes in professional practice and influenced requirements for licensure. We believe that these changes have not been detrimental to the profession but have aided in its advancement and general recognition. The increased number of prescriptions has brought increased revenue to the prescription department and increased the number of professional pharmacies. New drugs, appearing in ever increasing numbers, have likewise increased both the pharmacist's responsibilities and professional opportunities.

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THE ORGANIC CHEMIST (Continued from page 113)

the hydrogens of the amino group of benzedrine is replaced by a methyl group a product of somewhat lower pressor activity is obtained. Again the *d*-isomer is a rather powerful stimulant of the central nervous system.

The removal of the hydroxyl group from the para position of the phenyl group of epinephrine results in a product with some of the properties of both epinephrine and ephedrine.

The introduction of halogen in the phenyl group has not given any very effective compounds. The replacement of the phenyl nucleus by thiophene has resulted in a series of pressor substances, which however have no superiority and are more expensive to produce. Other major alterations in the basic structure of phenylethyl amine have been attempted, usually with indifferent success.

The earlier work of Barger and Dale[13] included a study of aliphatic amines wherein the amino group was on a terminal carbon atom. Believing that the differences exhibited between phenylethylamine and phenylisopropylamine might be due to the position of the amino group Rohrmann and Shonle[16] investigated a large series of aliphatic amines having both straight and branch chains in which the amino group was attached to other than the terminal carbon atom. Among the most active of these aliphatic amines was 2-amino heptane, "Tuamine,"[17] which is a very useful pressor drug because of its lack of central nervous stimulant effect. It can be prepared in a one-step synthesis by catalytically reducing 2-heptanone in the presence of ammonia:

$$CH_3CH_2CH_2CH_2CH_2COCH_3 + NH_3 + H_2 \rightarrow CH_3CH_2CH_2CH_2CH_2CHNH_2CH_3$$

Extensive chemical and pharmacological investigation of the aralkyl and alkyl amines has been carried on during the past third of a century but much work remains to be done before we can clearly understand the inter-relationships of structure and effect, which produce such different actions as pressor, depressor, central nervous stimulating, and analgesic. These different actions can be produced with but little change in relatively simple structures, a fact which gives us some indication of how highly specific are the actions of the body cells.

The field of sex hormones is full of interesting and complicated problems of organic chemistry. The hormones estrone, progesterone, testosterone and corticosterone are obtained either from natural sources or by modifying readily available steroids by devious and intricate chemical procedures.

The discovery of the synthetic estrogen diethylstilbestrol is an interesting example of how an investigator, working in one field, made an important discovery in another field. Dr. Dodds and his associates in England were working with synthetic polycyclic compounds capable of producing cancer in mice, studying the correlation of chemical structure to the intensity of the effect produced, in an endeavor to see if there was any connection with abnormal sterol metabolism. Since the ovarian hormones are believed to arise from the degradation of sterols, he wondered if his phenanthrene carcinogens had estrogenic activity and whether there was any physiological relationship between compounds which stimulate cells to grow malignantly and compounds which cause the cell proliferation which characterizes the estrous state.[18]

A low order of estrogenic activity was found when some of the potent carcinogenic compounds were tested, while some of the weaker carcinogens were found to be more active estrogens. As simple a compound as 4,4′-dihydroxydiphenyl was estrogenic. Even *p*-hydroxyphenylethyl alcohol was active. In extending this study, the compound anol, or *p*-hydroxyphenylpropylene was desired, and it was decided that it could most readily be prepared by the demethylation of a sample of the essential oil, anethole, which was at hand. The recrystallized anol was found to have high estrogenic activity.[19] However, on repeating this experiment samples of anol were obtained which had little or no activity.

Since the chemical properties of the active and inactive compound did not differ within the limits of experimental error, it seemed likely that the activity was due to the presence of a trace of an extremely potent estrogen. After a lot of patient investigation, the presence of a dihydroxystilbene derivative was detected. In 1939, it was ascertained by Dodds and his associates that the structure of the active component was α,α'-diethyl-4,4′-stilbenediol, and the correctness of the structure was proved by synthesis. This most potent estrogen could now be prepared synthetically instead of relying on the mere chance that one free radical would occasionally condense with another during the alkaline demethylation of anethol.

A long series of synthetic steps are still necessary for the preparation of this synthetic estrogenic compound, which was named diethyl stilbestrol.

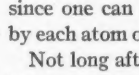
A new approach to the problem of designing synthetic drugs has been furnished by Pauling's theory that reactions of drugs in the living organism are related to the size and shape of the molecules involved.[20] A similar theory has been previously used to explain the specificity of enzyme action. It is believed that an enzyme acts on a particular substrate because portions of the enzyme molecule fit into the substrate molecule somewhat as a key fits a lock.

When an organic chemist makes a series of derivatives of a compound of known physiological activity in order to increase activity or lessen undesirable side effects, he may in fact be trying to learn which of the compounds produced fit best into the chemical structure of the biological system involved.

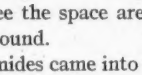
It is possible to replace a methyl group in some compounds with a chlorine atom without changing the response, whereas the hydrogen atom, which is chemically more like the methyl group, although smaller, cannot replace it. A recently reported study of the distance between the two oxygen groups in sex hormones[21] indicates that this distance is correlated with the degree of activity. The building of scale models of molecules often sheds much light on the problem since one can actually see the space areas filled by each atom of the compound.

Not long after sulfonamides came into use, the idea was advanced that this group of compounds acted by interfering with or blocking enzyme reactions vital to the life of the bacteria. When sulfanilamide is present, it is thought that the enzyme molecules combine with it instead of the *p*-aminobenzoic acid, a vitamin which is an essential metabolite that functions in one of the enzyme reactions necessary for the growth of the bacteria. Evidence for the correctness of this statement is provided by the fact that the bacteriostatic action of sulfanilamide can be blocked by an excess of *p*-aminobenzoic acid.

p-Aminobenzoic acid and sulfanilamide, while differing chemically, are rather closely related in molecular size and shape as shown below. Other examples could be given to support this theory.



p-Aminobenzoic acid



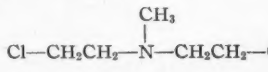
Sulfanilamide

Two compounds, identical in composition, but possessing different spacial arrangement of the atoms in the molecule, as is the case in optical isomers, may have different degrees of action or affect different centers. These facts show the extreme importance of the shape or configuration of the whole molecule in biological reactions, since they are asymmetric in character.

A Clue from Chemical Warfare

A great deal of biochemical research is being carried out here and abroad on organic chemical agents developed for use in warfare. It is of interest to note that substances of different chemical structure belonging to the same general class—for example, lachrymators or vesicants—have in addition potentialities as drugs, since they poison the same enzyme systems even though they may have very different chemical constitutions. It is the problem of the organic chemist and the biochemist to try to find the common denominator,[22] and to retain useful medical properties of such compounds while the undesirable properties are minimized.

Nitrogen mustards, such as methyl-bis-(beta-chloroethyl) amine,



highly toxic in themselves, in addition to being powerful warfare agents, have the property of destroying white blood cells more rapidly than normal tissue cells. This led to the biological and clinical investigation on the effects of these substances in Hodgkin's disease, leukemia, and lymphosarcoma.

Clinical investigations as yet do not show any permanent benefit when these diseases are treated with these compounds. However, this is a real lead which is being extended and investigated by closely cooperating teams of organic chemists, pharmacologists, pathologists, and clinicians.[23]

Isotopes and radioactive elements are now being incorporated into organic compounds. These compounds are used in tracer studies and, it is hoped, may also prove to be definite curative agents.

In tracer studies the compounds have served in several ways. For example, the fate of radioactive iodine in the body and of compounds containing it as a substituent can be readily determined, since the concentration of active iodine in any body tissue can be accurately and quickly determined. The distribution of iron in iron-deficient cells has been ascertained by giving drugs containing radioactive iron isotopes.

Tracer studies, in which constituents containing both stable isotopic hydrogen and nitrogen were used to follow the production of penicillin, pointed the way to the production of higher yields of penicillin-G, as well as to the production of many new penicillins. These new penicillins, now being prepared by a combination of organic and biological syntheses, are produced in crystalline state and in adequate amounts for screening tests. The organic chemist's problem is the synthesis of special broth constituents and the isolation and crystallization of the new penicillins.[24] In this, as in other investigations, the chemist's future work must be guided by the data obtained from the tests on the preceding products.

A search is continuously being made for a compound which will seek out and destroy cancer cells without harming the body cells. As yet, all attempts to find such a compound have met with failure. Attention is now being directed to organic compounds containing radioactive elements in the hope that some of these compounds may by some path or other find their way into the cancer cells where the rays emitted by the active element will act on the specific cell from within, much as the various rays now used act on them from without. The chemist's search is for a radioactive chemical key which will fit into the lock of the cancer cell.

Screening Tests

Specific investigations have originated from the systematic study of new derivatives of known active drugs or from the observations of investigators working in other fields or from fortuitous observations, and from systematic screening tests such as were carried out in malaria, where all compounds available were tested. There is an additional approach where new compounds of unique and unusual chemical structure are broadly screened for indications of pharmacological response and for action against bacteria, protozoa and virus. Today screening centers exist where new chemical compounds of miscellaneous structure are screened for effect in hypertension, schistosomiasis, cancer and many other metabolic disturbances and infections. In some of these cases a definite pattern is used for the type of compounds selected; in others the testing laboratory is interested in investigating almost any untested compound.

In subjecting new compounds of unusual chemical structure to broad screening tests the pharmacologist and biologist must use all their ingenuity and skill in devising and setting up the tests so that the maximum amount of information may be obtained from the sample available. If a compound gives evidence of possessing any useful activity, more of it may be prepared and subjected to detailed investigation, and the synthesis and study of closely related compounds begun.

In all these researches, the chemist must keep in close touch with the literature of his field of investigation. From his earliest graduate days, he has been trained to review and evaluate the published data which relates to his problem. A thorough literature search not only prevents duplication of work but brings to light investigations of others in similar and in related fields and furthermore often presents to the researcher ramifications of the problem which may result in a new approach or even a new project.

In addition to being thoroughly familiar with the published methods of preparation and the properties of the organic compounds being synthesized, the medicinal organic chemist needs to know whether the given compound or related compounds have been investigated previously in the laboratory or in the clinic. He will also need to be acquainted with the literature in related fields of pharmacology, biochemistry, bacteriology and parasitology, to understand better his problem and to discuss it more intelligently with his associates in these fields.

Organic chemical literature and the relationship of organic chemical compounds to the medical field are well covered by *Chemical Abstracts*. In addition, there are several additional medical, biological and pharmaceutical abstracts. Consequently, it is not too difficult a matter to locate most, if not all, of the data published about the compound. If, as occasionally happens, it has not been indexed, then one's imagination or the Ellery Queen instinct must dictate which indexed items may contain the information sought.

The continuous scanning of the current literature, accompanied by the abstracting and filing of pertinent items should not be neglected. This practice keeps the chemist well abreast of the current research projects in his own and related fields and forwards his research efforts in the same way as a thorough search of the past literature does. If the practice is kept up consistently it will eventually eliminate many future searches which he might otherwise have to make into the past literature.

Summary

From the examples given, it is evident that the methods that the organic chemist uses in cre-

ating new drugs are many and varied. Good training, a thorough knowledge of the literature, and close association with men working in the related fields of pharmacology, physiology, biology and experimental medicine are necessary.

The broad scope of the work of the organic chemist includes more efficient ways of producing drugs of proved value, the developing of synthetic procedures for the production of naturally occurring products and improving and modifying currently used drugs. The creation of new synthetic compounds may come from ideas arising from the consideration of natural products, from the search to improve known drugs, from research on other problems, from previous unsuccessful or partially worked problems, from erroneous theories, or from systematic pharmacologic and biologic surveys of large series of compounds.

Throughout all this work, unexpected relationships of structure to pharmacologic and biologic activity are continually being brought to light. Exploratory work in fundamental research must not be neglected, lest we have no foundations ready for further investigations. Vivid imagination, keen insight, untiring application, and unbounded enthusiasm are needed to bring a new drug to the bedside of the patient.

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THE BACTERIOLOGIST (Continued from page 125)

data on new products would be more acceptable as evidence if, in addition to clinical evidence, *in vitro* and *in vivo* laboratory tests reveal that an antiseptic displays constantly satisfactory low toxicity and high bactericidal efficiency by many different methods.

Salle and associates[9] have attempted to evaluate the antiseptic property of a new compound by comparing its toxicity for tissues and for pathogens. Combining *in vivo* and *in vitro* techniques, the highest dilution of the antiseptic required to kill living embryonic chick heart tissue is compared to the highest dilution required to kill the test organism (*Staphylococcus aureus* or other bacterium) under specified conditions, and this relationship is designated by a number called the "toxicity index." Theoretically the smaller the index the more nearly perfect the antiseptic, indicating the antiseptic's greater toxicity to the test organism than to the tissue.

In the method suggested by Welch and associates,[10] leucocytes are used as the tissue. Toxicity indices of antiseptics are determined by comparing their ability to kill the test organism (*Staphylococcus aureus*) with the ability to destroy the phagocytic activity of white blood cells. Hirsch and Novak[11] recommend a modification of this technique.

An infection-prevention test suggested by Nungester and Kempf[12] may provide a means of determining the value of a new compound in terms of its action on the skin as well as its effectiveness in preventing infection. The tail of a mouse is swabbed in a culture of the test organism (usually pneumococci) and then dipped separately into known dilutions of the antiseptic being tested. The latter is allowed to act for two minutes, during which time the abdomen of the mouse is prepared for incision. After two minutes, a half inch of the inoculated tail is cut off and inserted into the peritoneal cavity. The percentage of mice fatalities is used as an index of the effectiveness of the agent being tested. Sarber[13] suggests a modification of this technique, using the abraded skin of the abdomen instead of the tail, and using a culture of a hemolytic streptococcus as the test organism.

The method of Price[14] may be of value for certain new compounds. In this technique the human skin is employed, and a hand-scrubbing procedure tests "degerming" efficiency under conditions simulating actual practical conditions. The method of Novak and Hall[15] employs the abdominal skin area of a human subject for testing quantitatively the bactericidal efficiency of an antiseptic. Bost[16] recommends another technique in which the effectiveness of the antiseptic is tested on the human abdomen under actual surgical conditions. On the other hand the irritant effect of a new compound can be noted by the technique of Samuels[17] or modifications of this procedure.

In the writer's laboratory many of the above techniques are used. We also employ a simple perfusion technique[18] and a chick-embryo egg injection method.[19] Other *in vivo* procedures have been proposed to facilitate the evaluation of the antiseptic properties of a new drug.[20, 21, 22] If a new compound produces satisfactory findings by a few of these methods, it may be advisable to conduct a more extensive investigation, employing as many of the tests mentioned above as closely parallel actual practical conditions of use.

Testing Different Forms of a New Compound

While a compound in solution may itself have antiseptic properties, it may not necessarily be an effective antiseptic if marketed as an ointment, lotion, suppository, or other dosage form. An ingredient of the vehicle—such as a flavor, coloring, excipient, or filler—may reduce or completely inactivate the antiseptic properties of a new drug.

This must be recognized by testing a new antiseptic in the different forms in which it will be marketed and administered—as well as testing the drug in simple solution. At times this will require some special procedures. It must also be recognized that small batches made in the research laboratory may, on occasion, produce results different from that produced by batches made in the pilot plant or in large scale production.

In like manner, both experimental and production batches are tested after varying periods of storage at different temperatures to assure uniform stability of the preparation.

Internal Anti-Infectives

Obtaining bacteriologic evidence on the value of new anti-infectives for internal use is a still more difficult task and one that is more time consuming. Here we are concerned not only with

the efficiency of the product against microorganisms but more especially with its toxicity to the animal host which harbors the microorganisms.

The toxicity may be acute, chronic, and accumulative; and *in vivo* tests may require observations on both large and small animals with close study and careful evaluation by the bacteriologist, pharmacologist, pathologist, biochemist, toxicologist, clinician, and workers in other fields.

The various sulfonamides and the antibiotics, penicillin and streptomycin, represent examples of this group in which we have compounds that possess no pharmacological actions that are of therapeutic benefit other than the effects on bacteria. Frequently only large doses, even in the case of the sulfonamides, will produce significant toxicological effects and histological lesions in animal tissues. Yet clinical toxicity in humans occurs. *In vitro* tests, some of which are given above under antiseptics, may supply certain useful information, as they did in the case of the sulfonamides. For instance the latter were found to be only bacteriostatic; some were effective only against gram positive bacteria; others were effective only against gram negative bacteria; and a few sulfonamides displayed some bacteriostatic action against certain species in both groups.

In testing the bacteriostatic efficiency of the sulfonamides, the subculture tubes contain media with suitable quantities of para-aminobenzoic acid, the latter acting as the neutralizing agent for the sulfonamide drug which might be carried over.

With internal antiseptics, their action *in vivo* against experimental infections must be noted. The many details of observing and evaluating the *in vitro* and *in vivo* actions, especially of the sulfonamides, are beyond the scope of this discussion. They may be referred to in authoritative presentations by Long and Bliss,[23] Spink,[24] Mellon[25] and in the many annotated bibliographies and monographs on the sulfonamides available from various chemical and pharmaceutical manufacturers.

There are instances where new compounds showed little or no activity by *in vitro* tests, but were found to be efficient by *in vivo* tests. In the case of many protozoal infections, it may be difficult to determine experimentally the chemotherapeutic value of new compounds. Many of these etiological factors cannot be cultured, and *in vitro* tests are not applicable or suitable. In like manner, experimental animals commonly used are not susceptible to the human strains of certain etiological factors.

Antibiotics

Living organisms attempt to protect themselves against attack by their enemies in many different ways. In one of the latter procedures, they may produce and excrete specific substances that are antagonistic to or interfere with the metabolic processes of other organisms so that the latter are killed, completely repressed, or retarded in growth. It is this form of antagonism which is known today as antibiotic activity.

The bacteriologist's contribution to the development of new chemotherapeutic agents ordinarily begins after the research chemist has devised new chemical structures. In the case of antibiotics—as with biologicals—the bacteriologist himself makes the initial and primary contribution.

Penicillin was a chance discovery by the British bacteriologist Alexander Fleming, who recorded the antibiotic action of a penicillium colony while routinely examining culture plates of staphylococcus variants in his laboratory. Fleming later demonstrated that the antibacterial agent produced by the mold is very active against various types of bacteria and demonstrated that its toxicity upon injection into animals is very low. As early as 1929 Fleming believed that penicillin would be locally effective for therapeutic use.

Meanwhile, an American bacteriologist, Rene J. Dubos, and his associates conducted their pioneer researches in the field of antibiotics produced by soil organisms.[26] The approach here was based on the observation that all organic matter added to the soil eventually undergoes decomposition by microorganisms. It was hoped that by adding bacterial cultures to soil, a selective flora would be formed which would be capable of attacking the bacterial species added. This resulted in the identification of gramicidin and tyrocidine, antibiotics produced by the soil bacillus *B. brevis*. The mixture of the two related substances was called tyrothricin.

Later, tissue culture studies demonstrated the low local tissue toxicity of tyrothricin; on the other hand, animal studies showed a high toxicity by injection due to a hemolytic effect upon erythrocytes. Further investigation revealed the effectiveness of tyrothricin against a variety of gram positive organisms. This indicated its possibilities as an anti-infective for topical application, which were later confirmed by clinical

trial. Bacteriologic procedures for commercial production were worked out in regard to the nutrient medium, spore suspensions for inoculation, incubation method, and extraction and purification of the antibiotic.

The early work on tyrothricin revived interest in Fleming's observations on penicillin, which had lain dormant. The subsequent story of the tremendous amount of research that went into the development of penicillin is more or less familiar to every pharmacist. Cultivation of the mold and development of especially productive strains, large-scale culturing methods, assays, purification, biochemical studies, eventual identification of the different types of penicillin, and the laboratory synthesis of benzylpenicillin[27]—these and other research phases represented complex research problems, involving research workers from many fields but in which bacteriology has made one of its most notable contributions.

Even a cursory discussion of the problems and procedures involved in the development of penicillin would be beyond the space limitations of this discussion. For this information the reader may refer to the many books on the subject[28, 29, 30, 31, 32] as well as to the periodical literature and manufacturers' brochures.

Approach to Development of Streptomycin

While penicillin offered a remarkably effective action against a wide range of gram positive bacteria, there remained a need for a comparable drug that would be effective against gram negative bacteria. Such a drug, streptomycin, has only recently become generally available. Whereas penicillin was discovered more or less through chance by an alert bacteriologist, streptomycin resulted from a systematic and tedious investigation with well-defined objectives by a bacteriologist and microbiologist, Selman A. Waksman, and his associates.

The goal, as Waksman has explained,[33] was "an antibiotic substance capable of exerting a bacteriostatic and bactericidal effect upon gram negative bacteria, a substance active against these organisms not only in the test tube but also in the animal body, yet not very toxic or exerting otherwise undesirable effects upon the body, a substance not inactivated by the body fluids and therefore offering chemotherapeutic potentialities."

In the process of achieving this goal some thousands of actinomycetes, hundreds of fungi, and many bacteria were isolated from normal soils and from enriched soils, from composts, manures and peat bogs, as well as from other natural materials.

It was necessary to devise special bacteriologic methods for isolating antagonistic organisms and special techniques for producing, isolating and studying the antibiotics which they excreted.

From this work a number of antibiotic substances were produced, streptomycin eventually proving the most acceptable. It is interesting to note that the two cultures of the streptomycin-producing strain of *Streptomyces griseus*, from which the antibiotic was first isolated, were obtained from a heavily manured field soil and from the throat of a chicken.

As in the case of penicillin, there have been extensive coordinated studies by many investigators to bring streptomycin to full-scale production and to the patient. Studies on the medium for growing the actinomyces revealed marked effects on antibiotic activity by such factors as an acid reaction and the presence of glucose. In developing a method for isolating streptomycin from the culture broth the adsorption of streptomycin on various filters demonstrated the importance of selecting the proper filtration method. Testing streptomycin preparations for sterility involved use of methods to inactivate the antibiotic selectively, thus permitting an observable growth of any contaminant. The pharmacologist has been, and still is, concerned with elucidating the nature of erratic untoward reactions associated with streptomycin.

As investigations of these and other problems go forward there is accumulated an array of new knowledge that should expedite progress in the still embryonic field of antibiotics. Investigations are currently being conducted on antibiotics from other species of actinomyces, molds and bacteria, and also from the lichens, green algae, higher plants and other living matter.[34] The potentialities of nature appear great.

Microbiological Assays

Within recent years extensive investigations have been conducted on the growth requirements of bacteria, yeast and molds. We have noted the importance of such nutritional studies in assuring optimum growth of microorganisms that are used to produce antibiotics. By reversing the method of using such nutritional knowledge regarding microorganisms, we arrive at the microbiological technique of assay. That is, instead of supplying all requirements for optimum growth the medium is made suboptimal with respect to some specific growth

factor. By measuring the degree of growth of the test organism in the medium, one may indirectly measure (i.e., assay) the amount of the nutritional substance that is present at a suboptimal level.

This constitutes an interesting bacteriologic technique, made possible by studies that reveal specific growth factors for specific organisms. From such data may be formulated adequate nutritive media, using pure known chemical substances. The absence of any one of the known growth factors in the basal medium results in failure to support normal metabolism and growth. There is, accordingly, a direct relationship between the quantity of a substance present in an unknown suboptimal amount in the medium and the degree of growth of the microorganism.

For instance, certain members of the lactobacilli require pantothenic acid and riboflavin for growth, and the amount of lactic acid formed from glucose by these species depends especially upon the presence of these vitamins. Thus by employing a medium complete in all respects but deficient in pantothenic acid, it is possible to assay for pantothenic acid in a preparation under examination.

The microbiological assay procedure for niacin, biotin, riboflavin, and pantothenic acid is based upon the production of lactic acid by *Lactobacillus casei* and the determination of the amount of acid produced. In U. S. P. XIII the following notation under riboflavin tablets is of interest: "For purposes of legal control the results obtained by the Microbiological Assay shall prevail."

In like manner, the rate of fermentation of glucose by yeast (*Saccharomyces cervisiae*) with resultant production of alcohol and carbon dioxide, depends in large measure upon the amount of thiamine present. Yeast fermentation and the measurement of gas production can be and are used as a method of assaying thiamine.

The microbiological assay for folic acid is based on the growth of *Streptococcus lactis R* in a medium of known composition to which there has been added folic acid. The resultant turbidity (due to growth) is measured in a turbidimeter or nephelometer.

The growth of mold and the measurement by weight of the mycelia produced is employed as a microbiological technique in the assay of pyridoxine. At present, microbiological assay procedures are available for most of the vitamins of the B-complex group, for almost a dozen of the amino acids and even for potassium.[35]

Experience and skill in the performance of such assays are important factors. The extension of the practical use of these and other microbiological assays, for instance to protein hydrolysates, may serve a most useful purpose. New information will be obtained and discoveries in fundamental research will again triumph in that it may be possible to develop more useful medicinal products.

New Drugs Used Parenterally

Ampuls or injections represent a modern form of medication. They contain active medicaments for parenteral use and in some cases this route of administration is the only one applicable. The marketable product may be a sterile powder, a solution, or a suspension.

Conditions under which ampuls of new drugs are prepared and sterilized are the concern of the bacteriologist. The technique of sterilization used should not affect the potency or alter in any way the active therapeutic agents, but must be adequate to assure a sterile product. To determine the proper method necessitates an extended series of tests in which all commonly used techniques of sterilization are employed on different batches, and assay or potency tests are conducted in each instance before and after sterilization.

The procedure for testing the sterility of new drugs for parenteral use requires careful attention by a competent bacteriologist until a satisfactory procedure is assured. For instance in N. F. VIII under procedures for "Conducting Tests for Sterility" (which is the same as will be found in U. S. P. XIII), the statement is made that if substances under test are inherently bacteriostatic (such as the sulfonamides) or contain bacteriostatic agents (as is required for multiple-dose packages), they shall be treated with a suitable sterile inactivating agent or by adequate dilution in the culture medium. Since the latter procedure is not practical in large scale manufacturing, it may be necessary to conduct an extensive investigation to find a suitable inactivating or neutralizing agent. As examples, mention may be made of the use of para-aminobenzoic acid for neutralizing sulfonamides and the use of various penicillinase preparations (such as clarase) for the inactivation of penicillin.

It may be that a new drug can be, or should be, administered only in oily vehicles. The problem of making available a suitable procedure for determining the sterility of drugs in oils or fats is frequently very difficult.

Solutions of drugs administered parenterally, and especially intravenously, must be pyrogen-free. The bacteriologist is called upon to make such examinations upon the marketed preparation, if applicable, in accordance with accepted techniques found in N. F. VIII or the U. S. P. XIII.

In the preparation of a sterile product or a safe parenteral medicament, details of the care used throughout must be considered. Here the bacteriologist plays an important role in detailing the procedure of inspection and the methods employed in checking the equipment used in the sterilization technique.[36]

Bacteriostatic Agents

At times it becomes necessary to use a new bacteriostatic agent or a known bacteriostatic agent in a new product. This requires investigations to determine the usefulness and efficiency of a bacteriostatic agent in preventing the growth of bacteria, yeasts, and molds. This has been a frequent occurrence, especially during the war period when it became necessary to reduce the alcohol content and the sugar content of many products. The introduction of a wide variety of newer ointment and suppository bases, lotion vehicles, skin protectives, and the like also has frequently required the use of bacteriostatic agents, if the shelf-life of the preparations is to be prolonged.

It is well to point out here that the efficacy of the bacteriostatic agent to be used must be tested against a wide variety of different organisms. However, the bacteriologist should also isolate the microorganisms in the air or tanks in the production department where the preparations are to be manufactured. Tests should be carried out to observe the activity of the selected bacteriostatic agent against the organisms isolated. On more than one occasion the writer found that while a recommended bacteriostatic agent was effective when tested against stock strains of known species of organisms, the drug product became moldy or spoiled due to the presence of more resistant organisms as contaminants from the manufacturing process.

Sanitary Control

Drugs, new or old, must be produced under suitable sanitary control and marketed free from adulterants or deleterious substances. Bacteriological and microbiological analyses may be significant in determining the sanitary quality of raw materials, the plant sanitation during manufacturing procedures, and the sanitary quality of the final marketed products. The microscopist can detect filthy, putrid, or decomposed substances, insect parts, rodent contamination, and other extraneous substances.[37] The presence of molds and excessive bacterial counts indicate improper sanitary control. The presence of coliform bacteria in certain products may, when interpreted in proper perspective, help indicate possible sources of contamination.

Bacteriological examinations of certain oral preparations are being conducted today as an additional control measure. A low bacterial content indicates not only that proper sanitary supervision was practiced in the manufacture of the preparations under test, but it gives assurance of a longer shelf-life. Various manufacturers are conducting these examinations on such newer type preparations as oral whole proteins and oral protein hydrolysates, both in the finished product and frequently throughout the various stages of processing. Total bacterial counts and an examination for coliform bacteria are made, just as such tests are conducted on dairy products.

Ultraviolet irradiation and aerosol mists are now widely used for the sanitization of the atmosphere. Their function is to decrease contamination in the air during manufacturing and processing, during storage and packaging, and during testing procedures. To be assured that the techniques used are effective, it is necessary to determine whether the bacterial content of the atmosphere in different parts of the plant is actually lowered. Bacteriological examinations of the air before, during, and after the sanitizing operation will supply the necessary data. Periodic checks are carried out.

Finally, a competent bacteriologist can be of great service as a scientific detective or as a member of the trouble-shooting staff in most pharmaceutical manufacturing plants to identify any of the many possible contaminants and trace the offender to its source.

Conclusion

Space is inadequate to indicate, let alone detail, the many techniques of bacteriology and microbiology used in meeting various problems encountered in the discovery and development of new drugs. This brief presentation merely indicates in part the role that the bacteriologist and microbiologist plays today in bringing new medicinal preparations to the pharmacist and to the patient.

Such information, considered in relation to the contributions of other investigators, should give us a broader view of pharmacy. To the general practitioner of pharmacy, and through him to the practicing physician, it may provide a more comprehensive understanding of the firm scientific foundation upon which modern prescription medication rests.

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CLINICAL EVALUATION (Continued from page 135)

quasi-governmental or governmental agencies concerned with one or more phases of medical research has stemmed directly from this demand.

It appears almost inevitable that in any governmentally sponsored coordinating group for medical research a certain amount of direction by the group will be given to the investigator. Such direction may interfere with the freedom of the investigator and hence is repugnant to the true scientist. Furthermore, for various reasons, the pharmaceutical industry will find it difficult to conduct research on new drugs through such agencies.

There is a need, therefore, for an unofficial, independent body willing to assist in coordinating clinical research without interposing its will upon the investigator. Such a body has been established by the Council on Pharmacy and Chemistry of the American Medical Association in the Therapeutic Trials Committee. This Committee stands ready to assist the pharmaceutical manufacturer in securing competent clinical investigators to undertake clinical trials of new drugs. It also stands ready to assist clinical investigators by providing a means for coordinating clinical research between various institutions. This Committee has not been formed to supplant any existing groups interested in cooperative research; it wishes to supplement these facilities and lend support to the trends in clinical research that are already apparent.

Summary

The clinician is an indispensable cog in the machinery necessary for the development of new drugs. It is on the results of his work that the final decision as to the usefulness and safety of

the product is made. His task is difficult because of the complexities of his problems and the limitations imposed by the material with which he must work.

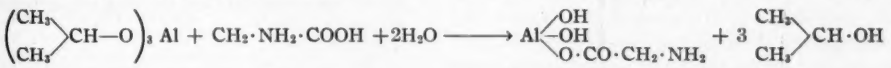
The clinical investigator is nowadays seldom a solitary worker but is the leader of a team of specialists ranging from physicists to statisticians. He is finding it advantageous to associate himself with colleagues in other institutions to broaden and hasten his attack on a problem.

Finally, the solution of a problem by the clinician often raises new problems which are referred back to the organic chemist, the biochemist, the pharmacologist or other laboratory scientists, thus initiating a new chain of investigations. This circle repeats itself many times, but like a wheel it rolls forward, ever advancing the frontiers of medicine.

THE PHARMACOLOGIST (Continued from page 129)

Let us now consider an extraordinary natural approach to a new drug. Among a team of research workers the pharmacologist had a gastrointestinal distress that was diagnosed as some erosion of the mucous membrane of the gastrointestinal tract just below the pyloris with some pylorospasm. During treatment of the hyperacidity he observed the lag in the relief of pain with aluminum hydroxide preparations. He was aware that aromatic spirit of ammonia gave instant relief of short duration. The thought of combining these effects in one molecule suggested itself.

In collaboration with the organic chemist of the group, after numerous unsuccessful attempts to unite an amine group with aluminum, the following reaction was employed successfully.



Was this substance a new chemical entity or just a mixture? The physical chemist of the group contributed his skill. The Al and N_2 contents of the molecule agreed well with theory. The water soluble glycine could not be washed out of the combination with water. Titration curves and measurements of a physiochemical character indicated the existence of a compound.

Next the physical chemist carried out titration curves on the new compound, aluminum dihydroxyamino acetate, in the presence of tenth-normal hydrochloric acid. These were compared with aluminum hydroxide and the former was shown to neutralize acid more rapidly. This was then tried on artificial gastric contents and the same rapid neutralizing power was found to obtain.

Of theoretical interest was the question, did the amino neutralize the acid first or did the glycine in the molecule activate the two remaining hydroxyl groups? It is well known that formaldehyde blocks amino groups and destroys their acid consuming power. In the presence of formaldehyde the acid neutralizing properties of the compound diminished greatly, indicating the value of the amino group in the molecule.

Could a combination of harmless glycine and aluminum hydroxide be toxic? Likely not, but one never knows. Acute toxicity experiments were done on dogs and rats. Chronic feeding studies were carried out on large numbers of rats in which the compound composed 5% of their entire food intake. These studies were conducted over several weeks and the animals' viscera were studied grossly and histologically. The substance proved to be innocuous.

Next, the selection of a critical gastroenterologist is in order. In consultation with the pharmacist, a suitable dosage form is decided upon. This is prepared in quantity by the pharmacist. The clinician gives the product to volunteers without gastrointestinal distress. The medication was asymptomatic. Then cautiously the drug is tried in hyperacidity and then in hyperacidity with ulcer. Here the efficacy of the compound as a gastric antacid is finally evaluated.

A new strategy in developing therapy against infectious diseases has been established by the discovery of antagonism between para-amino benzoic acid and the sulfonamide drugs. In this method the organism producing a disease is studied with respect to its nutritional and vitamin requirements. For example, the plasmodium of malaria thrives well *in vitro* on pantothenic acid. This is a lead. The organic chemist endeavors to prepare a masqueraded or disguised pantothenic acid derivative—a molecule in which the atoms spatially resemble pantothenic acid, yet with some substituent group that will cause an intracellular asphyxia of the organism. This has been partially accomplished by the syn-

thesis of pantothenic acid phenone. This new approach is logical and holds great promise for the future.

These illustrations serve to show the role played by the pharmacologist and toxicologist in the development of new drugs. Success is usually the result of team work, the concentration of many skills which unravels the mysteries of therapeutics and augments our materia medica.

PRODUCT DEVELOPMENT (Continued from page 147)

The pharmacist, however, in developing a dosage form for any new drug, must always guard against any unforeseen incompatibility.

Vaginal Suppositories

Vaginal suppositories usually are made in a base of glycerin and gelatin. This does not melt at body temperature, but gradually dissolves in the vaginal secretions. The vaginal suppository base contains water. Hence, the pharmacist, in developing a new product in this form, must know the compatibility of the new drug, so that the water present in the glycero-gelatin base does not react in the suppository mass in such a way as to destroy its therapeutic efficiency.

Conclusion

An effort has been made here to review for the dispensing pharmacist and hospital pharmacist the part played by the research pharmacist and pharmaceutical chemist in development of a new product. The properties of pharmaceutical elegance and pharmaceutical stability, which the dispensing pharmacist has a right to expect of the new product, are uppermost in his mind. Aside from the character of the product, however, the research pharmacist has a devotion to the ideal of integrity in his responsibility to humanity. The Honorable P. A. W. Self has summarized* eloquently the ideal research pharmacist and his ideals:

> [About the natural qualities which should be possessed by the ideal research worker] the first and most important of these is, of course, good judgment, and the next a vivid but well-controlled imagination. To these should be added great initiative, energy, and perseverance, some curiosity, and a good sense of proportion. The worker should be both a pessimist and an optimist, each in its right place. He should be sufficiently a pessimist to realize that some tasks are beyond him, and also that in almost all problems the difficulties are certain to be greater than they appear at first sight. He should be sufficiently an optimist to believe, once he has chosen his subject, that he is capable of overcoming any difficulties which may arise, however great they may be. In addition to all these qualities, if he is in the position of directing other workers he must possess a character which will ensure him at least the respect, or, still better, the devotion, of all his subordinates; he must be a good organizer, and also possess a considerable knowledge of human nature and its defects. In short, the ideal research worker would be a modern Solomon, free, of course, from the numerous distractions from which Solomon suffered, and also from the pessimism which appears to have attacked him in his later years.
>
> It is hardly necessary to say that, owing to the inevitable imperfections of human nature, such a being as I have described, possessing all the above qualities to the highest degree, has never existed and never will exist. At the same time, if we study the lives of some of the great scientists, I think that we shall be surprised how often this ideal has very nearly been attained.

* *British Pharmaceutical Journal and Pharmacist*, January 18, 1930, page 47. From an address delivered at a meeting of the Pharmaceutical Society of Great Britain.

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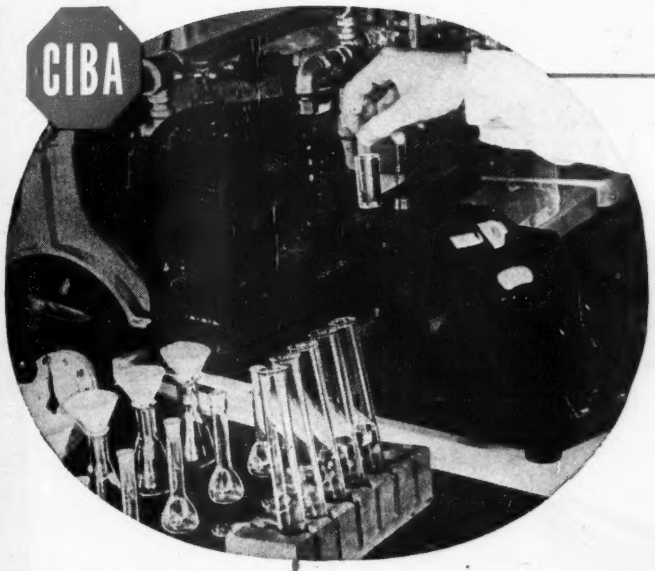

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Hematocrin

EACH **HEMATOCRIN** CAPSULE CONTAINS:

Ferrous Gluconate	(3 gr.)	0.194 gm.
Liver Concentrate	(1½ gr.)	0.097 gm.
Liver B Fraction	(1 gr.)	0.065 gm.
Thiamin Hydrochloride (B_1)		5.0 mg.
Riboflavin (B_2)		2.0 mg.
Niacinamide		10.0 mg.
Pyridoxine Hydrochloride (B_6)		0.1 mg.
Calcium Pantothenate		0.5 mg.
Ascorbic Acid (C)		30.0 mg.

Including components of the Vitamin B Complex present in Liver B Fraction and secondary anemia fraction of Whipple present in Liver Concentrate.

FAIR TRADED

AT FULL

LIST PRICE

BOTTLES OF 100

$4.25

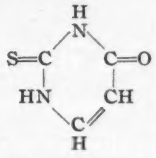
Harrower LABORATORY, INC · GLENDALE, CALIFORNIA

NNR

PRODUCTS RECENTLY ACCEPTED BY THE A. M. A. COUNCIL ON PHARMACY AND CHEMISTRY

Council descriptions of drug products are published regularly in THIS JOURNAL *as they are accepted. Rules upon which the Council bases its action appeared in the July (7:320) 1946 issue, and may be secured in pamphlet form upon request to the Secretary, Council of Pharmacy and Chemistry, American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.*

THIOURACIL.—2-Thiouracil.—$C_4H_4N_2OS$.—M. W. 128.15. The structural formula of thiouracil may be represented as follows:



Actions and Uses.—Thiouracil interferes with the formation of thyroxin by the thyroid gland. It is useful in the treatment of hyperthyroidism, thyrotoxicosis and thyroiditis. It is of no value and should not be used in other derangements of thyroid activity or in conditions not associated with hyperthyroidism.

Since thiouracil does not inactivate or interfere with the action of thyroxin already formed and stored in the gland, the effects of thiouracil medication do not appear until this store of thyroxin has been utilized. It may take several days to several weeks for the signs of decreased thyroid activity to become manifest, particularly if the patient has received previous iodine therapy.

Not all patients experience a permanent remission following thiouracil therapy, and the duration of treatment necessary to secure permanent relief from hyperthyroidism has not been determined. On the basis of the available information, it can be recommended only that thiouracil be used for preoperative treatment or for those patients for whom operation is contraindicated. The wisdom of depending on thiouracil as a substitute for operative procedure can be determined only by following the results of investigations carried on for longer periods.

Thiouracil produces adverse reactions in a high percentage of patients. The most frequent and severe complications of thiouracil therapy are granulocytopenia, leukopenia, drug fever and dermatitis. Jaundice, purpura and anemia have been reported following thiouracil therapy. The drug should be discontinued and appropriate therapy commenced immediately on the detection of signs of any of these complications.

Since the mild and the juvenile types of hyperthyroidism can frequently be controlled adequately by iodine therapy alone, thiouracil should not be used for these patients unless the safer form of therapy proves ineffective.

Dosage.—Initially 0.4 Gm. per day in divided doses, and after the symptoms are controlled or the basal metabolic rate is within the normal range the dose should be reduced to 0.1 or 0.2 Gm. per day.

Patients should be instructed to cease medication and report to their physician immediately if any adverse symptoms such as sore throat, fever, coryza or malaise are experienced.

Tests and standards.—

Thiouracil occurs as a crystalline powder having not more than a slight yellow tint or more than a slight odor and possessing a bitter taste. It melts about or somewhat above 300° C. It is slightly soluble in ethanol, very slightly soluble in water and in ether, and practically insoluble in chloroform and in benzene. The pH of a saturated aqueous solution of thiouracil is within the range 4.8–5.5.

For tests and standards see *J. Am. Med. Assoc.*, 133: 619, 1947.

ABBOTT LABORATORIES, NORTH CHICAGO, ILL.

Tablets Thiouracil: 0.1 Gm.

PARKE, DAVIS & CO., DETROIT

Tablets Thiouracil: 0.1 Gm.

WILLIAM H. RORER, INC., PHILADELPHIA

Tablets Thiouracil: 0.1 Gm.

E. R. SQUIBB & SONS, NEW YORK

Tablets Thiouracil: 0.1 Gm.

WINTHROP CHEMICAL CO., INC., NEW YORK

Tablets Thiouracil: 0.1 Gm.

VITAMIN B COMPLEX SYRUP (See New and Nonofficial Remedies, 1946, p. 618).

The following dosage form has been accepted:

MARVIN R. THOMPSON, CONNECTICUT

Vitamin B Complex Syrup: Each 5 cc. contains thiamine hydrochloride 1.5 mg., riboflavin 1.0 mg., pyridoxine hydrochloride 0.5 mg., niacin and niacinamide 7.0 mg., with other vitamin B complex factors as extracted from 10 Gm. of dried brewers' yeast.

THIAMINE HYDROCHLORIDE (See New and Nonofficial Remedies, 1946, p. 618).

The following dosage forms have been accepted:

THE HARROWER LABORATORY, INC., GLENDALE, CALIF.

Tablets Thiamine Hydrochloride: 10 mg.

THE VALE CHEMICAL CO., INC., ALLENTOWN, PA.

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

DEHYDROCHOLIC ACID (See New and Nonofficial Remedies, 1946, p. 352).

The following dosage forms have been accepted:

E. S. MILLER LABORATORIES, INC., LOS ANGELES

Tablets Dehydrocholic Acid: 0.243 Gm.

THE HARROWER LABORATORY, INC., GLENDALE, CALIF.

Tablets Dehydrocholic Acid: 0.24 Gm.

RIBOFLAVIN (See New and Nonofficial Remedies, 1946, p. 623).

The following dosage form has been accepted:

THE HARROWER LABORATORY, INC., GLENDALE, CALIF.

Tablets Riboflavin: 5 mg.

ASCORBIC ACID (See New and Nonofficial Remedies, 1946, p. 631).

The following dosage form has been accepted:

(*Continued on page 185*)

PENICILLIN-C.S.C.

in every dosage form the physician may need

PENICILLIN-C.S.C. ROMANSKY TYPE FORMULA

A sterile suspension of Crystalline Penicillin G Potassium in refined peanut oil and beeswax, containing 300,000 units of penicillin per cc.

Produces penicillin blood levels clinically effective in most cases for more than 24 hours from a single 1 cc. injection daily.

Supplied in 10 cc. rubber-stoppered serum-type vials containing 3,000,000 units of penicillin (300,000 units per cc.).

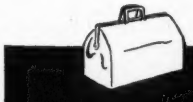
TABLETS BUFFERED PENICILLIN-C.S.C.

Tablets for oral administration, containing 50,000 units of Crystalline Penicillin G Potassium Salt. Destruction of contained penicillin by gastric acids is largely prevented by presence of glycerides and sodium salts of fatty acids. Supplied in bottles of 8 and 48 tablets.

CRYSTALLINE PENICILLIN G POTASSIUM SALT

Applicable for every condition in which penicillin is indicated, even when sodium penicillin appears undesirable. Especially advantageous for aerosol therapy. Purity not less than 1435* units per mg. Supplied in serum-type vials containing 100,000, 200,000 and 500,000 units.

THE many advantages of Penicillin-C.S.C. are kept constantly before the physician by continuous advertising in leading medical journals and an active direct mail program.



ALL CRYSTALLINE PENICILLIN SALTS...

ALL PENICILLIN G Clinically the most effective penicillin...

ALL HEAT STABLE...

NONE REQUIRE REFRIGERATION

CRYSTALLINE PENICILLIN G SODIUM SALT

Contains not less than 1500* units per mg. Effective against all penicillin sensitive organisms. Supplied in serum-type vials containing 100,000, 200,000 and 500,000 units.

*Variation in contained potency is due to difference in molecular weights of sodium and potassium.

C.S.C. Pharmaceuticals

A DIVISION OF

COMMERCIAL SOLVENTS CORPORATION

17 East 42nd St. CSC New York 17, N.Y.

E. S. MILLER LABORATORIES, INC., LOS ANGELES

Tablets Ascorbic Acid: 25 mg., 50 mg., 100 mg.

DIETHYLSTILBESTROL (See New and Nonofficial Remedies, 1946, p. 436).

The following dosage forms have been accepted:

THE HARROWER LABORATORY, INC., GLENDALE, CALIF.

Diethylstilbestrol (in Peanut Oil): 1.0 mg. per cc.: 1 cc. ampuls, and 5.0 mg. per cc.: 10-cc. vials, preserved with 0.5 per cent chlorobutanol.

E. S. MILLER LABORATORIES, INC., LOS ANGELES

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 1.0 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC., NEW YORK

Diethylstilbestrol (in Peanut oil): 0.5 mg. per cc. 1.0 mg. per cc. and 5.0 mg. per cc.: 1-cc. ampuls.

Vaginal Suppositories Diethylstilbestrol: 0.1 mg. and 0.5 mg. Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

THE VALE CHEMICAL CO., INC., ALLENTOWN, PA.

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 1.0 mg.

PENICILLIN IN OIL AND WAX (See *J. Am. Med. Assoc.*, Sept. 7, 1946, p. 23).

The following dosage forms have been accepted:

ABBOTT LABORATORIES, NORTH CHICAGO, ILL.

Penicillin (Calcium) in Oil and Wax: 300,000 units per cubic centimeter in B-D* 1-cc. glass cartridge with B-D Disposable Cartridge Syringe; and in B-D 1-cc. cartridge, with flushing fluid (benzyl alcohol 1.5 per cent in isotonic solution of sodium chloride), for use in B-D Cartridge Syringe. Calcium penicillin suspended in peanut oil containing 4.8 per cent (*w/v*) white wax, U. S. P.

THE WM. S. MERRELL CO., CINCINNATI

Penicillin (Calcium) in Oil and Wax: 300,000 units per cubic centimeter, 10-cc. vials. Calcium penicillin suspended in peanut oil containing 4.8 per cent white wax, U. S. P.

WYETH INCORPORATED, PHILADELPHIA

Tubex Penicillin (Calcium) in Oil and Wax: 300,000 units per cubic centimeter. Penicillin calcium suspended in peanut oil containing 4.8 per cent yellow wax, U. S. P.

Trademark registered, Becton, Dickinson & Co.

A. Ph. A. HOLDS MIDWEST DISTRICT MEETING

PHARMACISTS of Iowa, Minnesota, Nebraska, North Dakota and South Dakota will convene at the Hotel Paxton in Omaha, Neb., Wednesday, April 23, to attend the first district meeting to be held by the AMERICAN PHARMACEUTICAL ASSOCIATION. The one day session is being conducted according to a plan proposed by President Earl R. Serles and approved by the Council of the ASSOCIATION. There will be a two hour program in the morning, a luncheon meeting, and a two hour program in the afternoon.

President E. R. Serles of the A. PH. A. will preside and make a brief introductory address. Other speakers at the morning session will be Dr. Robert P. Fischelis of Washington, D. C., secretary and general manager of the ASSOCIATION, who will speak on "Pharmacy in the Affairs of the Nation." He will be followed by Dr. Melvin W. Green, director of the laboratory of the AMERICAN PHARMACEUTICAL ASSOCIATION, who will speak on "Progress in the Science of Pharmacy." These addresses will be followed by an open forum with members of the ASSOCIATION and others in attendance participating.

Dean Hugh C. Muldoon of the College of Pharmacy of Duquesne University, who is chairman of the House of Delegates of the A. PH. A., will be the luncheon speaker. His address will be a highlight of the occasion, as the meeting is to be held during National Pharmacy Week and Dr. Muldoon will emphasize the pharmacist's importance in the field of national health affairs.

The afternoon session will be addressed by Professor Louis C. Zopf of the College of Pharmacy of the University of Iowa, who is chairman of the Scientific Section of the A. PH. A. He will speak on "Progress in the Art of Pharmacy." His address will cover the latest developments in prescription practice and extemporaneous preparation of dosage forms of drugs.

Following Prof. Zopf's address, there will be a round-table discussion with all speakers participating in answering questions from the audience.

All pharmacists, whether members of the AMERICAN PHARMACEUTICAL ASSOCIATION or not, are cordially invited to attend the meeting and participate in the discussions.

The object of the plan to hold district meetings is to bring to members of the AMERICAN PHARMACEUTICAL ASSOCIATION, in districts distant from the annual convention site, a report of progress in the affairs of the A. PH. A. and new developments in the art and science of pharmacy.

FROM THE SECRETARY'S JANUARY DIARY

—2nd—

IT IS good to have everyone back on the job, for busy weeks lie ahead of us. Dues are coming in with every mail. The records are being made and membership certificates and cards dispatched as promptly as the limited staff, working many hours overtime, can accomplish the task. Much of today getting ready for the meeting of the Publications Committee tomorrow. To Hogate's for dinner with Treasurer Schaefer, who is also chairman of the Committee on Legislation. All evening reviewing the next steps to be taken in the field of barbiturate control.

—3rd—

For the all-day meeting of the Committee on Publications came Chairman Beal, Dean Christensen, Hugo Schaefer and the Secretary. First a general discussion of the JOURNALS, the N. F. and the Recipe Book with Editors Powers, Sonnedecker and Green giving their views and reviews; next the executive session for passing upon the program to be submitted to the Council; and finally the outline for the Committees' report and recommendations. A full day well spent, with a brief intermission for a sandwich luncheon served at the building. In the evening to dinner with Council and Publications Chairman Beal at the Occidental, and later preparing the agenda for the coming Council meeting with him at the Washington Hotel.

—4th—

Today a meeting with Chairman Hansen and Editor Francke of the American Society of Hospital Pharmacists to discuss plans for the establishment of a Hospital Pharmacy Division in the A. PH. A. administrative setup, for the purpose of increasing services to hospital pharmacists.

—5th—

All this Sunday at the office, and during the afternoon another two hour conference with the hospital group out of which came a finished plan of action for submission to the Council.

—6th—

A visit from Senior Pharmacists Kinsey and Foster of the U. S. Public Health Service apropos of the coming examination for candidates for commissions as pharmacists in the United States Public Health Service.

At lunch with J. S. Mordell exchanging data of use in the Pharmaceutical Survey, which is now in the midst of gathering the raw material from which recommendations will be distilled. Later in the day and far into the night preparing reports for submission to the Council.

—7th—

A visit from W. O. McCarthy of Merck & Co., discussing displays. Most of the afternoon going over Pharmaceutical Survey data with Director E. C. Elliott, and it appears that he has amassed and digested a tremendous amount of factual material.

—8th—

At luncheon with Assistant Surgeon-General R. C. Williams of the U. S. Public Health Service, Dr. E. C. Elliott and J. S. Mordell of the Pharmaceutical Survey to determine how manpower can be provided for all concerned. Later much telephone conversation on the proposed amendment to the Food, Drug and Cosmetic Act to require pre-testing of streptomycin.

—9th—

Addressed the Traveler's Auxiliary of the D. C. Pharmaceutical Association at their monthly luncheon at the Mayflower. C. F. Baker presides ably over this progressive group.

—10th—

This day at Trenton to sit with the Committee on Food and Drugs of the State Department of Health to review testimony showing violation of the milk standards and then to put finishing touches on a proposal outlining minimum standards for clinical laboratories.

—11th and 12th—

This week end in Washington meeting Douglass Poteat to discuss A. PH. A. and American Cancer Society cooperation. Also interviewing many potential candidates for stenographic and clerical positions. All day Sunday at the office completing important Council business.

—13th—

A visit today from Assistant Director Hullerman of the American Hospital Association to discuss plans for the second Institute on Hospital Pharmacy. And it seems the first Institute was so thoroughly successful that annual repetitions are indicated. Chicago in May seems likely at this writing

—15th—

All day with the auditors who come annually to inspect the books and verify the accounts. Late in the afternoon to have an aching tooth removed and then to retire with an ice cap, which kept things fairly comfortable without benefit of pills.

—17th—

Most of the day finishing reports and charts for the Council meeting with little time for anything else.

—18th—

Early to Baltimore for an all-day meeting of the American Council on Pharmaceutical Education made doubly interesting by the presence of Dr. E. C. Elliott, who gave a preview of his findings on certain educational investigations for the benefit of the thinking of the Council. Dr. Elliott believes that some situations in pharmacy and pharmaceutical

education that are uncovered should be met at once and not be subjected to a waiting period until the Survey has been completed. This makes sense and the Council is bestirring itself.

—19th—

All day finishing the final budget report, and in the evening to Baltimore meeting Treasurer Schaefer for dinner at the Belvidere and then to Dr. Dunning's home for the meeting of the Committee on Finance with Swain, Dunning and Schaefer (the full Committee) present. The final report represents intensive study and emphasis on service to pharmacy and to the members of the ASSOCIATION rather than the accumulation of idle funds.

—20th—

Members of the Council began arriving early for the two day meeting. All but one of the sixteen on hand and deeply interested in the reports and proceedings. During the luncheon recess an opportunity to inspect the building and facilities with all the staff at their accustomed tasks. Following the afternoon session a dinner at the Statler and further business thereafter.

—21st—

An early meeting of the Council at the Statler with the chief order of business the approval of the largest budget in the history of the ASSOCIATION. Following unanimous disposal of the budget came the recommendations and proposals of President Serles, and much additional business after the luncheon and before adjournment at 4:30 p. m. In the evening addressed a group of D. C. science librarians at A. PH. A. Headquarters on "How We React to Drugs," and then to the Statler for conferences with members of the Council scheduled to depart tomorrow.

—22nd and 23rd—

Disposing of routine assignments following the Council meetings, and then a series of conferences with President Serles who is staying over for the meetings of the American Council on Education on Friday and Saturday. Agreed upon programs for proposed district meetings, addresses to state conventions, the general program for the Milwaukee convention, and student branch activities.

—24th—

Today a meeting of the American Council on Education to consider the compulsory military training program, Federal aid to education, and at night, following a dinner at the Mayflower, a discussion of the present status of the United Nations Educational, Scientific and Cultural Organization. Pharmaceutical education is concerned with all of these.

—25th—

Another meeting of the American Council on Education—this time to consider the proposal to create in the Federal government a Department of Education, Health and Welfare, headed by a cabinet officer. It seems the educators, like the health professions, want a separate department but will settle

one of the oldest and most reliable Protections against Infection

For cuts, abrasions and minor wounds suggest Official 2%

IODINE

PREPARATIONS

MILD TINCTURE OF IODINE U.S.P. XII

Mild Tincture of Iodine may be prepared as follows:

Iodine .....20 Gm.
Sodium Iodide .....24 Gm.
Diluted Alcohol, a sufficient quantity, to make .....1000 cc.

Dissolve the iodine and sodium iodide in a sufficient quantity of diluted alcohol to make product measure 1000 cc.

SOLUTION OF IODINE U.S.P. XII

Iodine .....20 Gm.
Sodium Iodide .....24 Gm.
Distilled Water, a sufficient quantity, to make.....1000 cc.

Dissolve the iodine and sodium iodide in 50 cc. of distilled water, then add sufficient distilled water to make the product measure 1000 cc.

Iodine Educational Bureau, Inc.

120 Broadway, New York 5, N.Y.

Efficiency can add up to *100%* by *Integrated action* ....

In this emotionally conditioned post-war period, your physicians have increasing need for a therapeutic agent to allay spastic conditions incidental to gastro-intestinal disturbances.

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Our current advertising to physicians features a timely product, the components of which have increased efficiency by their integrated action.

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containing

Homatropine Methylbromide

Alukalin

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PROVIDING **3** *IMPORTANT*

THERAPEUTIC VALUES

ANTISPASMODIC
ANTACID ADSORBENT
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for

GASTROINTESTINAL
DYSFUNCTIONS

LUSYN is available at your wholesalers in bottles of 100 TABLETS

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for a prominent place in a tripartite setup. Bidding good-bye to President Serles who had attended the Education Council meetings during the past two days.

—29th—

Attending mid-winter meeting of N. J. Pharmaceutical Association and in the evening officiating as toastmaster at the annual dinner which was well attended. The speaking program was over in thirty minutes.

—30th—

This day in Baltimore with Treasurer Schaefer and the auditors checking the ASSOCIATION Securities. After the latter half of the afternoon at the Washington office, a delightful dinner party at the Mayflower with Bob Gasen of Bristol Laboratories as host and Drs. Hyde and Romansky of U. S. P. H. S., Captain Wilcox, U. S. N. and others among the guests.

—31st—

All morning conferring with officials and consultants of the International Education Institute and found A. G. Murray of F. D. A. the other representative of pharmacy called in for advice on scholarships and placement of foreign students in U. S. colleges.

R

ERA OF GROUP PRACTICE IN HOSPITALS FORESEEN

A new era marked by gradual changes in the fundamental form of medical practice has been predicted for the near future by Dean W. C. Rappleye of Columbia University's College of Physicians and Surgeons. He foresees the general community hospital as the future center of all health services.

This type of group practice would have a particular bearing upon the important question of proper distribution of physicians, Dr. Rappleye believes. The first five to ten years of practice by young physicians is considered a manpower waste, since their time is only partly occupied during this period. Larger practices are available in smaller rural communities, Dr. Rappleye explained, but the young physician does not practice there because modern facilities, such as group hospital practice offers, are not now available.